

REMARKS

Applicants confirm the election of Group I, claims 1-9 drawn to compounds and composition in the restriction requirement and the election of species made in the paper dated 10/21/2004. As a result of the present amendment, claims 1-8 have been amended, compound claims 15 & 16 have been added. The species in new claims 15 & 16 are generically embraced by the instant generic claims. Claims 1-16 are pending in this application. No new matter has been added to this application by way of amendment.

FORMAL REQUIREMENTS

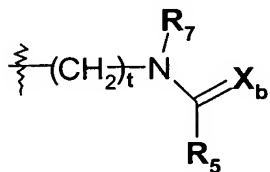
Claims 1-8 have been objected to in the Office Action for the reasons provided therein.

Applicants have addressed the issues raised by the Examiner in the present amendment. Withdrawal of the objections is therefore respectfully requested.

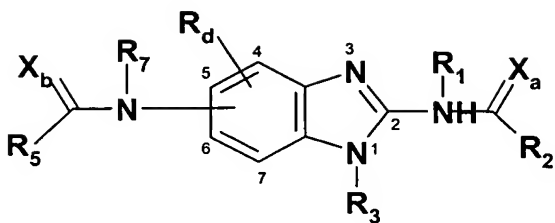
CLAIM REJECTIONS

Claims 1-3, 7 and 9 have been rejections under 35 USC 102(a) as allegedly being anticipated by Fang et al (2-Aminobenzimidazoles as Neuropeptide Y Y5 Antagonists: Solution Phase Synthesis and Structure Relationships, ACS National Meeting, Chicago, IL, August 26, 2001) and Frenkel et al. (US 2003/0144286).

Applicants' amendment to claims where the instant R₄ is limited to



wherein t = 0 renders moot the rejection. The instant formula(I) compounds are therefore limited to

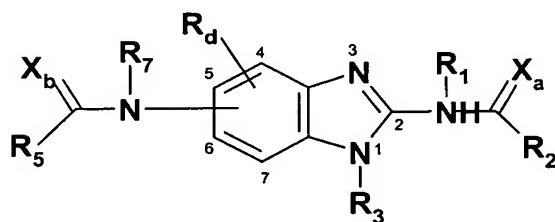


. In contrast, both Fang and Frenkel et al require a methylene group between the benzimidazole ring and their respective R group possessing a nitrogen atom. Withdrawal of the rejection is therefore respectfully requested.

Claims 1-9 have been rejected under 35 USC 103(a) as allegedly being unpatentable over Frenkel et al. (US 2003/0144286), Craig et al. (US 3,336,191), Craig et al. (US 3,401,171), Chow et al. (US 3,401,173), Grier (US 4,011,236) and Smith Kline & French Labs (GB 1,122,957) each taken alone or in combination. This rejection is traversed, in-part.

Applicants contend that the prior art of record, either alone or in combination, does not teach or suggest all the limitations of the instant claims.

As indicated above, the instant claims are directed to compounds of the formula(I) where the R₄ substituent is the group possessing R₅ attached to the benzo ring (exemplified below), where the nitrogen atom being directly linked to the benzo ring:



The compounds of the invention possess anti- Itk kinase activity, and are therefore taught in the present specification as being useful for treating diseases and pathological conditions involving inflammation, immunological disorders and allergic disorders. Applicants have also claimed benefit to US provisional application 60/402,009 filed

08/08/2002. Each of the currently listed claims have full support in their respective embodiments found in applicants' priority document.

The Frenkel et al reference has a publication date of 7/31/2003, with an application filing date of 10/9/2002 and a claimed priority date of 10/9/2001. The priority date of the instant claims is 08/08/2002, before both the publication date and application filing date of Frenkel. Therefore the Frenkel et al publication does not qualify as prior art under 35 USC 102(a). Applicants would also like to point out that the compounds in the published application relied upon by the Examiner to establish the prior art rejection are not present in the Frenkel priority document (provided herewith as 'Exhibit A'), US provisional no. 60/327,818, see Figs 1a – 1e. Nor is there any teaching of synthetic examples for such compounds, see provisional pages 32-47.

The Craig et al. (US 3,336,191), Craig et al. (US 3,401,171), and Smith Kline & French Labs (GB 1,122,957) references disclose benzimidazole type compounds alleged to possess antihelmintic activity. In contrast, the activity of the instant compounds is anti-Itk kinase as explained above. Moreover, each of the prior art documents broadly disclose an infinite number of compounds with preferred embodiments and species diverging structurally from those of the instant claims. This is seen in the prior art where R on the benzimidazole nitrogen is preferred to be hydrogen, and the benzo ring Y, Z substituents are either not present or are smaller groups substituted on both 5 and 6 positions of the benzimidazole ring. In contrast, the instant claims select single (5 or 6) substitution on the benzimidazole ring, and the instant R₃ is optionally substituted alkyl. Thus, in view of the structural divergence combined with the different compound activities, the alleged requisite motivation in the prior art is not present.


Chow et al. (US 3,401,173), also discloses benzimidazole compounds alleged to possess antihelmintic activity. The Chow definitions of X do not structurally fall within the analogous position of the instant compounds which require an R⁵-C(O)-(R⁷)-N- or R⁵-C(S)-(R⁷)-N-.

Grier (US 4,011,236) teaches benzimidazole compounds shown to be useful as UV absorbing materials. None of the compounds, generically or specifically disclose substitution on the benzimidazole benzo ring.

I view of the foregoing withdrawal of the obviousness rejection over the present claims is proper and respectfully requested.

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EXHIBIT A

BENZIMIDAZOLE DERIVATIVES

BACKGROUND OF THE INVENTION

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The recruitment of immune cells to sites of injury involves the concerted interactions of a large number of soluble mediators. Several cytokines appear to play key roles in these processes, particularly IL-1 and TNF. Both cytokines are derived from mononuclear cells and macrophages, along with other cell types. Physiologically, they produce many of the same proinflammatory responses, including fever, sleep and anorexia, mobilization and activation of polymorphonuclear leukocytes, induction of cyclooxygenase and lipoxigenase enzymes, increase in adhesion molecule expression, activation of B-cells, T-cells and natural killer cells, and stimulation of production of other cytokines. Other actions include a contribution to the tissue degeneration seen in chronic inflammatory conditions, such as stimulation of fibroblast proliferation, induction of collagenase, *etc.* They have also been implicated in the process of bone resorption and adipose tissue regulation. Thus, these cytokines play key roles in a large number of pathological conditions, including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, diabetes, obesity, cancer, sepsis, *etc.*

The importance of IL-1 in inflammation has been demonstrated by the ability of the highly specific IL-1 receptor antagonist protein (IL-1Ra, or IRAP) to relieve inflammatory conditions (for review, *see, e.g.,* Dinarello (1997) *Cytokine Growth Factor Rev.* 8:253-265).

IL-1 treatment of cells induces the formation of a complex consisting of the two IL-1 receptor chains, IL-1R1 and IL-1RAcP, and the resulting heterodimer recruits an adaptor molecule designated as MyD88 (Wesche *et al.* (1999) *J. Biol. Chem.* 274:19403-19410). MyD88 binds to a protein designated IRAK (IL-1 receptor associated kinase) (*see, O'Neill et al.* (1998) *J. Leukoc. Biol.* 63(6):650-657, Auron (1998) *Cytokine Growth Factor Rev.* 9(3-4):221-237 and O'Neill (2000) *Biochem. Soc. Trans.* 28(5):557-563, for reviews). IRAK is subsequently phosphorylated and released from the receptor complex to interact with a tumor necrosis factor receptor-associated factor, TRAF6, which transduces the signal to downstream effector molecules (Cao *et al.* (1996) *Nature* 383:443-446). TRAF6 can trigger the NIK/IKK kinase cascade to activate the

transcription factor NF- κ B. NF- κ B regulates a number of genes that, in turn, regulate immune and inflammatory responses.

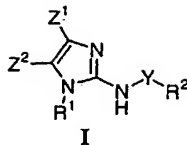
Four IRAKs have been identified: IRAK-1 (Cao, *et al.* (1996) *Science* 271:1128-1131), IRAK-2 (Muzio, *et al.* (1997) *Science* 278:1612-1615), the monomyeloic cell-specific IRAK-M, also known as IRAK-3 (Wesche, *et al.* (1999) *J. Biol. Chem.* 274:19403-10) and IRAK-4 (PCT Publication No. WO 01/051641). IRAK proteins have been shown to play a role in transducing signals other than those originating from IL-1 receptors, including signals triggered by activation of IL-18 receptors (Kanakaraj *et al.* (1999) *J. Exp. Med.* 189(7):1129-1138) and LPS receptors (Yang *et al.* (1999) *J. Immunol.* 163:639-643; Wesche *et al.* (1999) *J. Biol. Chem.* 274:19403-19410). Overexpression of IRAK-2 and IRAK-M has been shown to be capable of reconstituting the response to IL-1 and LPS in an IRAK deficient cell line.

The identification of compounds that modulate the function of IRAK proteins represents an attractive approach to the development of therapeutic agents for the treatment of inflammatory and immune-related conditions and diseases associated with IRAK-mediated signal transduction, such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, diabetes, obesity, allergic disease, psoriasis, asthma, graft rejection, cancer and sepsis.

SUMMARY OF THE INVENTION

The present invention is directed to compounds which modulate interleukin-1 (IL-1) receptor-associated kinase (IRAK) and are useful in the prevention or treatment of inflammatory and immune-related conditions and diseases. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of the subject compounds and compositions in the prevention or treatment of conditions or diseases mediated by IRAK.

The compounds provided herein have the general formula (I):



wherein

R^1 is selected from the group consisting of H, (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl and heteroaryl;

R^2 is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, perfluoro(C₁-C₄)alkyl, aryl or heteroaryl;

Y is C(O), S(O)_m, S(O)₂NR', C(O)NR', CR³R⁴, C(NR'), C(=CR³R⁴), CR³(OR') or CR³(NR'R''), wherein the subscript m is an integer from 1 to 2;

Z^1 and Z^2 are independently H, halogen, CN, CO₂R', CONR'R'', (C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, perfluoro(C₁-C₄)alkyl, aryl, heteroaryl, NR'R'' or OR''; alternatively, Z^1 and Z^2 may be combined to form an additional fused 5-, 6-, 7- or 8-membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring;

R' and R'' are independently H, (C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl or aryl(C₁-C₄)alkyl;

alternatively, when R' and R'' are attached to nitrogen, R' and R'' may be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring; and

alternatively, when Y is CR³R⁴, C(NR'), C(=CR³R⁴), CR³(OR') or CR³(NR'R''), R³, R⁴ or R' may be combined with R² to form a 5-, 6-, 7- or 8-membered ring containing from 0 to 3 heteroatoms selected from the group consisting of O, N, Si and S.

Unless otherwise indicated, the compounds provided in the above formula are meant to include pharmaceutically acceptable salts and prodrugs thereof.

The present invention also provides pharmaceutical compositions comprising a compound of formula I in combination with a pharmaceutically acceptable carrier or excipient.

The present invention further provides methods for treating or preventing a condition or disorder mediated by IRAK comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides exemplary structures of preferred compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION**Abbreviations and Definitions**

The abbreviations used herein are conventional, unless otherwise defined.

As used herein, the term "IRAK" refers to an interleukin-1 (IL-1) receptor-associated kinase protein or variant thereof that is capable of mediating a cellular response to IL-1 *in vitro* or *in vivo*. IRAK may be kinase-active or kinase-inactive. Exemplary kinase-inactive IRAKs include IRAK-1 and IRAK-4. Exemplary kinase-active IRAKs include IRAK-2 and IRAK-3 (also known as IRAK-M). Kinase-active IRAKs may be capable of transphosphorylation of other proteins or autophosphorylation. In preferred embodiments, IRAK is IRAK-1 and/or IRAK-4.

IRAK variants include proteins substantially homologous to native IRAK, *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, IRAK derivatives, homologs and fragments). The amino acid sequence of an IRAK variant preferably is at least about 80% identical to a native IRAK, more preferably at least about 90% identical, and most preferably at least about 95% identical.

The terms "signal transduction", "signaling" and related terms refer to a process whereby an extracellular signal (*e.g.*, the concentration of a cytokine, hormone, neurotransmitter, growth factor) is transmitted via a cascade of intracellular protein-protein interactions to the cell nucleus and generates one or more cellular responses (*e.g.*, gene transcription, protein secretion, mitosis, apoptosis). The interaction of an extracellular signaling molecule (*e.g.*, a cytokine, a hormone, a neurotransmitter, a growth factor) with one or more transmembrane protein receptors at the cell surface can activate one or more signal transduction pathways. The protein-protein interactions in a signal transduction pathway may be multivalent and include covalent and/or non-covalent protein modification. An intracellular signaling molecule, *i.e.*, a signal transducing protein or a signal transducer, may be involved in one or more signal transduction

pathways. As described herein, protein-protein interactions includes direct and indirect interactions.

The terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

5 The terms "prevent", "preventing" and "prevention" refer to a method of barring a subject from acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include reducing a subject's risk of acquiring a disease.

As used herein, the phrase "IRAK-mediated condition or disorder" and related phrases and terms refer to a condition or disorder characterized by inappropriate, *e.g.*, less than or greater than normal, IRAK activity. Inappropriate IRAK functional activity might arise as the result of IRAK expression in cells which normally do not express IRAK, increased IRAK expression or degree of intracellular activation (leading to, *e.g.*, inflammatory and autoimmune disorders and diseases) or decreased IRAK expression. An IRAK-mediated condition or disorder may be completely or partially
10 mediated by inappropriate IRAK functional activity. However, an IRAK-mediated condition or disorder is one in which modulation of IRAK results in some effect on the underlying condition or disorder (*e.g.*, an IRAK inhibitor results in some improvement in patient well-being in at least some patients).

The term "therapeutically effective amount" means the amount of the
20 subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "modulate" refers to the ability of a compound to increase or decrease the function and/or expression of IRAK, where IRAK function may include
25 kinase activity and/or protein-binding. Modulation may occur *in vitro* or *in vivo*. Modulation, as described herein, includes the inhibition or activation of IRAK function and/or the downregulation or upregulation of IRAK expression, either directly or indirectly. A modulator preferably activates IRAK function and/or upregulates IRAK expression. More preferably, a modulator activates or inhibits IRAK function and/or
30 upregulates or downregulates IRAK expression. Most preferably, a modulator inhibits IRAK function and/or downregulates IRAK expression. The ability of a compound to inhibit IRAK function can be demonstrated in an enzymatic assay or a cell-based assay (*e.g.*, inhibition of IL-1-stimulated NF- κ B activation).

The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

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The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e. C₁-C₈ means one to eight carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers.

The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Similarly, the term dialkylamino refers to an amino group having two attached alkyl groups that can be the same or different.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl

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group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. When a prefix such as (C_2-C_8) is used to refer to a heteroalkyl group, the number of carbons (2-8, in this example) is meant to include the heteroatoms as well. For example, a C_2 -heteroalkyl group is meant to include, for example, $-\text{CH}_2\text{OH}$ (one carbon atom and one heteroatom replacing a carbon atom) and $-\text{CH}_2\text{SH}$. The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkyleneedioxy, alkyleneamino, alkylene diamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Thus, the terms "cycloalkyl" and "heterocycloalkyl" are meant to be included in the terms "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl", are meant to include alkyl substituted with halogen atoms which can be the same or different, in a number ranging from one to $(2m'+1)$, where m' is the total number of carbon atoms in the alkyl group. For example, the term "halo(C_1-C_4)alkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Thus, the term "haloalkyl" includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl

substituted with halogen atoms in a number ranging from two to $(2m'+1)$ halogen atoms, where m' is the total number of carbon atoms in the alkyl group). The term "perhaloalkyl" means, unless otherwise stated, alkyl substituted with $(2m'+1)$ halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term "perhalo(C_1 - C_4)alkyl", is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl and 8-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like), including those alkyl groups in which the alkyl group is a heteroalkyl group.

Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical, unless otherwise indicated. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups

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selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''',
 -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-
 C(O)NR''R''', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -
 S(O)R', -S(O)₂R', -S(O)₂NR'R'', -CN and -NO₂ in a number ranging from zero to
 5 (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'' and R'''
 each independently refer to hydrogen, unsubstituted (C₁-C₈)alkyl and heteroalkyl,
 unsubstituted aryl, aryl substituted with 1-3 halogens, alkoxy or thioalkoxy groups, or
 aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they
 can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For
 10 example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above
 discussion of substituents, one of skill in the art will understand that the term "alkyl" in
 its broadest sense is meant to include groups such as haloalkyl (e.g., -CF₃ and -CH₂CF₃)
 and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like). Preferably, the alkyl
 groups will have from 0-3 substituents, more preferably 0, 1, or 2 substituents, unless
 15 otherwise specified.

Similarly, substituents for the aryl and heteroaryl groups are varied and are
 selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R',
 -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR''R''',
 -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R',
 20 -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a
 number ranging from zero to the total number of open valences on the aromatic ring
 system; and where R', R'' and R''' are independently selected from hydrogen,
 (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C₁-
 C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl.

25 Two of the substituents on adjacent atoms of the aryl or heteroaryl ring
 may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein
 T and U are independently -NH-, -O-, -CH₂- or a single bond, and the subscript q is an
 integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl
 or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-
 30 B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -
 S(O)₂NR'- or a single bond, and the subscript r is an integer of from 1 to 3. One of the
 single bonds of the new ring so formed may optionally be replaced with a double bond.
 Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may
 optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where the

subscripts s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is hydrogen or unsubstituted (C₁-C₆)alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O),
5 nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition
10 salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be
15 obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric,
20 hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and
25 the like (see, for example, Berge *et al.* (1977) *J. Pharm. Sci.* 66:1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner.
30 The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds

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that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound of the invention.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Description of the Embodiments

The present invention is directed to compounds, compositions and methods useful in the modulation of IRAK. Accordingly, the compounds of the present invention are compounds which inhibit at least one function or characteristic of a mammalian IRAK polypeptide, for example, a human IRAK polypeptide.

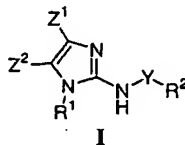
The full-length human IRAK-1 protein (GenBank Accession No. L76191) has been described, see, *e.g.*, Cao *et al.* (1996) *Science* 271(5252):1128-1131, and has the sequence shown in SEQ ID NO:1. IRAK-1 is an active protein kinase and is capable of autophosphorylation *in vitro*. However, it has been shown that the enzymatic activity is not required for an IRAK-mediated cellular response to IL-1, *e.g.*, IL-1-stimulated NF- κ B activation. IRAK-4 (GenBank Accession No. AX196260) is described in PCT Publication No. WO 01/051641 and has the sequence shown in SEQ ID NO:2.

15 IRAK Modulators

The present invention provides compounds having antiinflammatory and anti-immunoregulatory activity. It is believed that the compounds of the invention will interfere with inappropriate IL-1 induced signal transduction by specifically modulating or inhibiting IRAK function, *e.g.*, IRAK-1 and/or IRAK-4 function. IRAK is an intracellular component of the signaling pathway that is activated by the binding of IL-1 to the IL-1 receptor (IL-1R). In particular, IRAK associates with the active receptor complex and transduces the IL-1 signal by interacting with one or more intracellular signaling molecules. Cellular responses to IRAK-mediated signal transduction include increased transcription of genes that regulate inflammatory and immune responses, *e.g.*, NF- κ B. Therefore, inhibition of IRAK function, *e.g.*, inhibition of IRAK kinase activity, will inhibit an IRAK-mediated cellular response and treat or prevent an IRAK-mediated condition or disorder.

While a precise understanding of the mechanism by which compounds of the present invention inhibit an IRAK-mediated response is not required in order to practice the present invention, it is believed that the compounds interfere with the phosphorylation by IRAK of one or more intracellular proteins, including IRAK itself. Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein.

The compounds provided herein have the general formula (I):



In formula I, R¹ is H, (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl or heteroaryl.

R² is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, perfluoro(C₁-C₄)alkyl, aryl or heteroaryl.

Y is C(O), S(O)_m, S(O)₂NR', C(O)NR', CR³R⁴, C(NR'), C(=CR³R⁴), CR³(OR') or CR³(NR'R''), wherein the subscript m is an integer from 1 to 2.

Z¹ and Z² are independently H, halogen, CN, CO₂R', CONR'R'', (C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, perfluoro(C₁-C₄)alkyl, aryl, heteroaryl, NR'R'' or OR'.

Alternatively, Z¹ and Z² may be combined to form an additional fused 5-, 6-, 7- or 8-membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring.

R³ and R⁴ are independently H, CN, CO₂R', CONR'R'', (C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl, heteroaryl, NR'R'' or OR'.

R' and R'' are independently H, (C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl or aryl(C₁-C₄)alkyl.

Alternatively, when R' and R'' are attached to nitrogen, R' and R'' may be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring.

Alternatively, when Y is CR³R⁴, C(NR'), C(=CR³R⁴), CR³(OR') or CR³(NR'R''), R³, R⁴ or R' may be combined with R² to form a 5-, 6-, 7- or 8-membered ring containing from 0 to 3 heteroatoms selected from the group consisting of O, N, Si and S.

In one group of preferred embodiments, Z¹ and Z² are combined to form an additional fused aryl, cycloalkyl or heterocycloalkyl ring. Particularly preferred are those embodiments in which Z¹ and Z² are combined to form an additional fused aryl ring. Preferably, the aryl ring is a benzene ring. Other particularly preferred embodiments are those in which Z¹ and Z² are combined to form an additional fused cycloalkyl ring. Preferably, the cycloalkyl ring is a cyclohexyl ring. Still other particularly preferred

embodiments are those in which Z^1 and Z^2 are combined to form an additional fused heterocycloalkyl ring. Preferably, the heterocycloalkyl ring is a tetrahydropyranyl ring.

In another group of preferred embodiments, Y is selected from the group consisting of $C(O)$, $S(O)_m$ and CR^3R^4 .

5 In another group of preferred embodiments, Y is $C(O)$.

In another group of preferred embodiments, Y is $S(O)_m$, wherein the subscript m is an integer selected from 1 to 2. In particularly preferred embodiments, Y is SO_2 .

In another group of preferred embodiments, Y is CR^3R^4 .

10 In separate, but preferred embodiments, R^1 is H.

In another group of preferred embodiments, R^1 is (C_1-C_8) alkyl or (C_1-C_8) heteroalkyl. Particularly preferred are those embodiments in which R^1 is substituted (C_1-C_8) alkyl or substituted (C_1-C_8) heteroalkyl. Particularly preferred substituents are OR' , $NR'R''$, $OC(O)R'$, CO_2R' , $CONR'R''$, $OC(O)NR'R''$, $NR''C(O)R'$ or $NR''CO_2R'$.

15 Further preferred are those embodiments in which R^1 is substituted with OH.

In another group of preferred embodiments, R^1 is cycloalkyl or heterocycloalkyl. Particularly preferred are those embodiments in which R^1 is substituted cycloalkyl or substituted heterocycloalkyl. Particularly preferred substituents are OR' , $NR'R''$, $OC(O)R'$, CO_2R' , $CONR'R''$, $OC(O)NR'R''$, $NR''C(O)R'$ or $NR''CO_2R'$.

20 Further preferred are those embodiments in which R^1 is substituted with OH. Particularly preferred cycloalkyl and heterocycloalkyl groups are cyclohexyl and tetrahydropyranyl groups, respectively.

In a separate group of preferred embodiments, R^2 is aryl or heteroaryl. Particularly preferred are those embodiments in which aryl is substituted phenyl.

25 In another group of embodiments, R^2 is aryl, Z^1 and Z^2 are combined to form an additional fused aryl ring and Y is $C(O)$.

In another group of preferred embodiments, R^1 is substituted (C_1-C_8) alkyl or substituted (C_1-C_8) heteroalkyl, R^2 is aryl, Z^1 and Z^2 are combined to form an additional fused aryl ring and Y is $C(O)$.

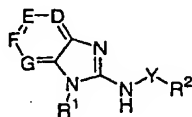
30 In another group of preferred embodiments, R^1 is substituted (C_1-C_8) cycloalkyl or substituted (C_1-C_8) cycloheteroalkyl, R^2 is aryl, Z^1 and Z^2 are combined to form an additional fused aryl ring and Y is $C(O)$.

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In yet another group of preferred embodiments, R^1 is substituted (C₁-C₈)alkyl or substituted (C₁-C₈)heteroalkyl, R^2 is substituted phenyl, Z^1 and Z^2 are combined to form an additional fused benzene ring and Y is C(O).

In one group of preferred embodiments, the compounds have the formula

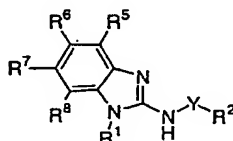
5 (II):



II

In formula II, D, E, F and G are independently CR''' and N, wherein each R''' is independently selected from H, halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, cycloalkyl(C₁-C₄)alkyl, heterocyclo(C₁-C₄)alkyl, aryl, aryl(C₁-C₄)alkyl, heteroaryl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' and N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R''' may be combined with R¹ or an adjacent R''' to form an additional 5-, 6-, 7- or 8-membered ring. R¹, R², Y, R' and R'' are as defined for general formula I.

15 In another group of preferred embodiments, the compounds have the formula (IIa):



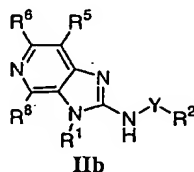
IIa

In formula IIa, R⁵, R⁶, R⁷ and R⁸ are independently H, halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl, aryl(C₁-C₄)alkyl, heteroaryl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR', or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2. Alternatively, R⁵, R⁶, R⁷ or R⁸ may be combined with an adjacent R group selected from the group consisting of R¹, R⁵, R⁶, R⁷ and R⁸ to form an additional 5-, 6-, 7- or 8-membered ring. R¹, R², Y, R' and R'' are as defined for general formula I.

25 Particularly preferred are those embodiments in which R¹ is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl,

aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl or heteroaryl; and R⁹ is halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R⁶ may be combined with R⁵ or R⁷ to form an additional 5-, 6-, 7- or 8-membered ring. R' and R'' are as defined for general formula I.

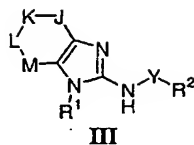
In another group of preferred embodiments, the compounds have the formula (IIb):



wherein

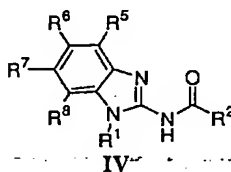
R⁵, R⁶ and R⁸ are independently H, halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl, aryl(C₁-C₄)alkyl, heteroaryl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2. Alternatively, R⁶ may be combined with R⁵ to form an additional 5-, 6-, 7- or 8-membered ring. Alternatively, R⁸ may be combined with R⁷ to form an additional 5-, 6-, 7- or 8-membered ring. R¹, R², Y, R' and R'' are as defined for general formula I. Particularly preferred are those embodiments in which R¹ is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocycloalkyl(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl or heteroaryl; and R⁶ is halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or combined with R⁵ to form an additional 5-, 6-, 7- or 8-membered ring.

In another group of preferred embodiments, the compounds have the formula (III):



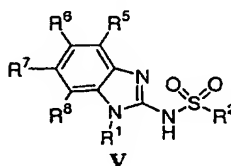
In formula III, J, K, L and M are independently CR^aR^b, NR^a and O, wherein R^a and R^b are independently H, halogen, CN, CO₂R', CONR'R'', (C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl, heteroaryl, NR'R'' or OR'. Alternatively, J, K, L or M may be combined with an adjacent R group selected from R¹, R^a and R^b to form an additional 5-, 6-, 7- or 8-membered ring. R¹, R², Y, R' and R'' are as defined for general formula I.

In another group of preferred embodiments, the compounds have the formula (IV), where R¹, R², R⁵, R⁶, R⁷ and R⁸ are as defined above:



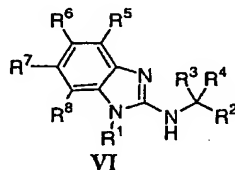
Particularly preferred are those embodiments in which R¹ is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl or heteroaryl; and R⁶ is halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R⁶ may be combined with R⁵ or R⁷ to form an additional 5-, 6-, 7- or 8-membered ring. R' and R'' are as defined for general formula I.

In another group of preferred embodiments, the compounds have the formula (V), where R¹, R², R⁵, R⁶, R⁷ and R⁸ are as defined above:



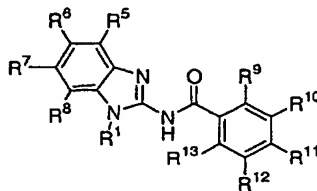
Particularly preferred are those embodiments in which R^1 is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl or heteroaryl; and R^6 is halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R^6 may be combined with R^5 or R^7 to form an additional 5-, 6-, 7- or 8-membered ring. R' and R'' are as defined for general formula I.

In another group of preferred embodiments, the compounds have the formula (VI), where R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as defined above:



Particularly preferred are those embodiments in which R^1 is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl or heteroaryl; and R^6 is halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R^6 may be combined with R^5 or R^7 to form an additional 5-, 6-, 7- or 8-membered ring. R' and R'' are as defined for general formula I.

In another group of preferred embodiments, the compounds have the



formula (VII):

In formula VII, R^9 , R^{10} , R^{11} , R^{12} and R^{13} are independently H, halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl, aryl(C₁-C₄)alkyl,

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heteroaryl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2. Alternatively, R⁹, R¹⁰, R¹¹, R¹² or R¹³ may be combined with an adjacent R group selected from the group consisting of R⁹, R¹⁰, R¹¹, R¹² and R¹³ to form an additional 5-, 6-, 7- or 8-membered ring. R¹, R⁵, R⁶, R⁷, R⁸, R' and R'' are as defined above. Particularly preferred are those embodiments in which R¹ is (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl or heteroaryl; and R⁶ is halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR' or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R⁶ may be combined with R⁵ or R⁷ to form an additional 5-, 6-, 7- or 8-membered ring. R' and R'' are as defined for general formula I.

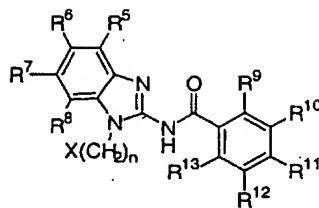
Preferred compounds are those in which R¹ is (C₁-C₈)alkyl or (C₁-C₈)heteroalkyl. In certain preferred embodiments, R¹ is substituted (C₁-C₈)alkyl or substituted (C₁-C₈)heteroalkyl. In certain preferred embodiments, R¹ is (C₁-C₈)alkyl substituted with OR', NR'R'', OC(O)R', CO₂R', CONR'R'', OC(O)NR'R'', NR''C(O)R' or NR''CO₂R'. In certain preferred embodiments, R¹ is (C₁-C₈)alkyl substituted with OH.

In still other preferred compounds, R¹ is cycloalkyl or heterocycloalkyl. In certain preferred embodiments, R¹ is substituted cycloalkyl or substituted heterocycloalkyl. In certain preferred embodiments, R¹ is cycloalkyl substituted with OR', NR'R'', OC(O)R', CO₂R', CONR'R'', OC(O)NR'R'', NR''C(O)R' or NR''CO₂R'. In certain preferred embodiments, R¹ is cycloalkyl substituted with OH. In other preferred embodiments, R¹ is cyclohexyl or tetrahydropyranyl.

Other preferred compounds are those in which at least one of R⁹, R¹⁰, R¹¹, R¹² and R¹³ is NO₂.

Exemplary structures within this preferred group of embodiments are shown in FIG. 1.

In another group of preferred embodiments, the compounds have the formula (VIIa):



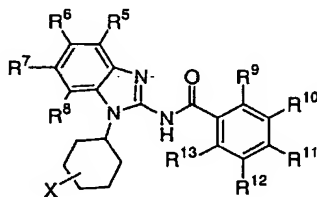
VIIa

In formula VIIa the subscript n is an integer from 1 to 5, X is OR', NR'R'', OC(O)R', CO₂R', CONR'R'', OC(O)NR'R'', NR''C(O)R' or NR''CO₂R' and R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are as defined above. In certain preferred

embodiments, X is OH.

In certain preferred embodiments, at least one of R⁹, R¹⁰, R¹¹, R¹² and R¹³ is NO₂.

In another group of preferred embodiments, the compounds have formula (VIIb), where X, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are as defined above:

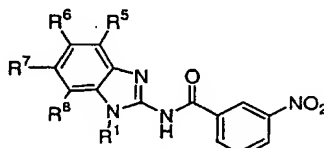


VIIb

In certain preferred embodiments, X is OH.

In certain preferred embodiments, at least one of R⁹, R¹⁰, R¹¹, R¹² and R¹³ is NO₂.

In another group of preferred embodiments, the compounds have the formula (VIIc), where R¹, R⁵, R⁶, R⁷, and R⁸ are as defined above:



VIIc

Preferred compounds are those in which R^1 is (C_1-C_8) alkyl or (C_1-C_8) heteroalkyl. In certain preferred embodiments, R^1 is substituted (C_1-C_8) alkyl. In certain preferred embodiments, R^1 is (C_1-C_8) alkyl substituted with OR' , $NR'R''$, $OC(O)R'$, CO_2R' , $CONR'R''$, $OC(O)NR'R''$, $NR''C(O)R'$ or $NR''CO_2R'$. In certain

5 preferred embodiments, R^1 is (C_1-C_8) alkyl substituted with OH.

In still other preferred compounds, R^1 is cycloalkyl or heterocycloalkyl. In certain preferred embodiments, R^1 is substituted cycloalkyl. In certain preferred embodiments, R^1 is cycloalkyl substituted with OR' , $NR'R''$, $OC(O)R'$, CO_2R' , $CONR'R''$, $OC(O)NR'R''$, $NR''C(O)R'$ or $NR''CO_2R'$. In certain preferred embodiments,

10 R^1 is cycloalkyl substituted with OH. In other preferred embodiments, R^1 is cyclohexyl or tetrahydropyranyl.

In each group of embodiments above, embodiments in which R^1 is (C_1-C_8) alkyl, hetero (C_1-C_8) alkyl, fluoro (C_1-C_4) alkyl, cycloalkyl (C_1-C_8) alkyl, heterocyclo (C_1-C_8) alkyl, aryl, aryl (C_1-C_8) alkyl, arylhetero (C_1-C_8) alkyl or heteroaryl; and R^6 is halogen, (C_1-C_4) alkyl, perfluoro (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl (C_1-C_4) alkyl, CN, CO_2R' , $CONR'R''$, $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$, $S(O)_mNR'R''$, $S(O)_mR'$ or $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1 to 2, or R^6 may be combined with R^5 or R^7 to form an additional 5-, 6-, 7- or 8-membered ring are particularly preferred.

20 The vast majority of the compounds contemplated for use in the present invention are novel, while some are available from commercial sources. The present invention specifically contemplates the exclusion of commercially available compounds from the compound claims (and, if appropriate, from the pharmaceutical composition claims). Unless otherwise indicated, it is to be understood that the invention includes

25 those compounds that are novel, as well as pharmaceutical compositions, various methods (e.g., methods of treating or preventing certain IRAK-mediated conditions and diseases), and the like which include both the novel compounds of the invention and compounds that are commercially available. Exemplary commercially available benzimidazoles include nocodazole, carbendazim, mebendazole, albendazole, benomyl, thiabendazole,

30 fenbendazole, oxfendazole and flubendazole.

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Synthesis of IRAK Modulators

Synthesis routes to the compounds provided herein are described in the Examples. One of skill in the art will appreciate that the substituents (*e.g.*, R', R'', R''', *etc.*) can be altered before, during or after preparation of the heterocyclic scaffolding and that suitable adjustments in the exemplary conditions (*e.g.*, temperatures, solvents, *etc.*) can be made. Additionally, one of skill in the art will recognize that protecting groups may be necessary for the preparation of certain compounds and will be aware of those conditions compatible with a selected protecting group.

Compositions

In another aspect, the present invention provides pharmaceutical compositions for modulating IRAK. The compositions comprise a compound of the present invention with a pharmaceutically acceptable carrier or excipient.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients (and in the specified amounts, if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant that the carrier or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In one embodiment, the invention provides the subject compounds combined with a pharmaceutically acceptable excipient such as sterile saline, methylcellulose solutions, detergent solutions or other medium, water, gelatin, oils, *etc.*

The compounds or compositions may be administered alone or in combination with any convenient carrier, diluent, *etc.*, and such administration may be provided in single or multiple dosages. Useful carriers include water soluble and water insoluble solids, fatty acids, micelles, inverse micelles, liposomes and semi-solid or liquid media, including aqueous solutions and non-toxic organic solvents. All of the above formulations may be treated with ultrasounds, stirred, mixed, high-shear mixed, heated, ground, milled, aerosolized, pulverized, lyophilized, *etc.* to form pharmaceutically acceptable compositions.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared

by any of the methods well known in the art. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,256,108; 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are

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5 suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

15 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

20 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

25 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for

example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, *etc.*, containing the compounds of the present invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.

The pharmaceutical compositions and methods of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment or prevention of the above mentioned pathological conditions.

Methods of Use

The compounds and compositions of the present invention can be used to treat and/or prevent conditions and disorders associated with IL-1 signaling, such as inflammation, cancer and various immune disorders. These conditions or disorders

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include, but are not limited to: (1) inflammatory or allergic diseases such as systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies and food allergies, (2) inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vaginitis, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria and pruritus, (5) vasculitis, (6) spondyloarthropathies, (7) scleroderma, (8) asthma and respiratory allergic diseases such as allergic asthma, allergic rhinitis, hypersensitivity lung diseases and the like, (9) autoimmune diseases, such as arthritis (including rheumatoid and psoriatic), multiple sclerosis, systemic lupus erythematosus, type I diabetes, glomerulonephritis and the like, (10) graft rejection (including allograft rejection and graft-v-host disease), and (11) other diseases in which undesired inflammatory responses are to be inhibited, such as atherosclerosis, myositis, neurodegenerative diseases (*e.g.*, Alzheimer's disease), encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, allergic conjunctivitis, otitis, chronic obstructive pulmonary disease, sinusitis, Behcet's syndrome and gout.

Preferably, the present methods are directed to the treatment of diseases or conditions selected from rheumatoid arthritis, inflammatory bowel disease, allergic disease, psoriasis, asthma, multiple sclerosis, graft rejection and sepsis. More preferably, the present methods are directed to the treatment of rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis.

In preferred embodiments, the present invention provides methods of treating or preventing an IRAK-mediated condition or disorder by administering to a subject having such a condition or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions. In one group of embodiments, diseases or conditions, including chronic diseases, of humans or other species can be treated with inhibitors of IRAK function.

Depending on the disease to be treated and the subject's condition, the compounds of the present invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. The present

invention also contemplates administration of the compounds of the present invention in a depot formulation, in which the active ingredient is released over a defined time period.

5 In the treatment or prevention of inflammatory and immune-related conditions and diseases or other conditions or diseases mediated by IRAK, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 10 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the 15 patient to be treated. The compounds may be administered on a regimen of, for example, 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability 20 and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The compounds of the present invention can be combined with other compounds having related or complementary utilities to prevent and treat inflammatory 25 and immune-related conditions and diseases, including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and those pathologies noted above. In some embodiments, such combination therapy is used in the treatment or prevention of a condition or disorder mediated by IRAK.

For example, the present compounds may be used in conjunction with an 30 antiinflammatory or analgesic agent such as an opiate agonist, a lipoxxygenase inhibitor, such as an inhibitor of 5-lipoxxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 (COX-2) inhibitor, an interleukin inhibitor, such as an interleukin-1 receptor antagonist, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-

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5 suppressing antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sulindac, tenidap, and the like. Similarly, the instant compounds may be administered with an analgesic listed above; a potentiator such as caffeine, an H₂-antagonist (*e.g.*, ranitidine), simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a diuretic; and
10 a sedating or non-sedating antihistamine.

Likewise, compounds and compositions of the present invention may be used in combination with other drugs that are used in the treatment, prevention, suppression or amelioration of the conditions or diseases for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an
15 amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include
20 those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound of the present invention. Examples of other therapeutic agents that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists, (b) corticosteroids, such as beclomethasone, methylprednisolone, betamethasone, prednisone, prednisolone, dexamethasone, fluticasone and
25 hydrocortisone, and corticosteroid analogs such as budesonide; (c) immunosuppressants such as cyclosporine (cyclosporine A, *Sandimmune*®, *Neoral*®), tacrolimus (FK-506, *Prograf*®), rapamycin (sirolimus, *Rapamune*®) and other FK-506 type immunosuppressants, and mycophenolate, *e.g.*, mycophenolate mofetil (*CellCept*®); (d)
30 antihistamines (H₁-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cypheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-

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- asthmatics such as β_2 -agonists (*e.g.*, terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (*e.g.*, zafirlukast, montelukast, pranlukast, iralukast, pobilukast and SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005);
- 5 (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (*e.g.*, alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid and tioxaprofen), acetic acid derivatives (*e.g.*, indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac,
- 10 fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin and zomepirac), fenamic acid derivatives (*e.g.*, flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (*e.g.*, diflunisal and flufenisal), oxicams (*e.g.*, isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (*e.g.*, acetyl salicylic acid,
- 15 sulfasalazine and analogs, mesalamine) and the pyrazolones (*e.g.*, apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone and phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (*Celebrex*®) and rofecoxib (*Vioxx*®); (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) interleukin inhibitors, such as interleukin-1 (IL-1) inhibitors, and chemokine receptor antagonists; (j) cholesterol lowering agents
- 20 such as HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and other statins), bile acid sequestrants (*e.g.*, cholestyramine and colestipol), nicotinic acid (niacin), fibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzaifibrate), probucol and nitroglycerin; (k) anti-diabetic agents such as insulin, sulfonyleureas (*e.g.*, glyburide, meglitinide), biguanides, *e.g.*, metformin (*Glucophage*®),
- 25 α -glucosidase inhibitors (acarbose), thiazolidinone compounds, *e.g.*, rosiglitazone (*Avandia*®), troglitazone (*Rezulin*®) and pioglitazone (*Actos*®); (l) preparations of interferon beta (interferon β -1 α , interferon β -1 β); (m) gold compounds such as auranofin and aurothioglucose, (n) etanercept (*Enbrel*®), (o) antibody therapies such as orthoclone (OKT3), daclizumab (*Zenapax*®), basiliximab (*Simulect*®), infliximab (*Remicade*®) and
- 30 D2E6 TNF antibody, (p) lubricants or emollients such as petrolatum and lanolin, (q) keratolytic agents, (r) vitamin D₃ derivatives, *e.g.*, calcipotriene or calcipotriol (*Dovonex*®), (s) PUVA, (t) anthralin (*Drithrocreme*®), (u) etretinate (*Tegison*®) and isotretinoin, (v) multiple sclerosis therapeutic agents such as interferon β -1 β

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(Betaseron®), interferon β -1 α (Avonex®), azathioprine (Imurek®, Imuran®), glatiramer acetate (Capoxone®), a glucocorticoid (e.g., prednisolone) and cyclophosphamide and (w) β 3 adrenergic receptor agonists, leptin or derivatives thereof, and neuropeptide Y (e.g., NPY5) antagonists; (x) other compounds such as 5-aminosalicylic acid and prodrugs thereof; (y) DNA-alkylating agents (e.g., cyclophosphamide, ifosfamide), antimetabolites (e.g., azathioprene, 6-mercaptopurine, methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disruptors (e.g., vincristine, vinblastine, paclitaxel, colchicine, nocodazole and vinorelbine), DNA intercalators (e.g., doxorubicin, daunomycin and cisplatin), DNA synthesis inhibitors such as hydroxyurea, DNA cross-linking agents, e.g., mitomycin C, and hormone therapy (e.g., tamoxifen, and flutamide). The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In still other particularly preferred embodiments, the present methods are directed to the treatment of rheumatoid arthritis, wherein the compound of the invention is administered either alone or in combination with a second therapeutic agent selected from methotrexate, sulfasalazine, a COX-2 inhibitor, hydroxychloroquine, cyclosporine A, D-penicillamine, infliximab, etanercept, auranofin and aurothioglucose. When used in combination, the practitioner can administer a combination of the therapeutic agents, or administration can be sequential.

In yet other particularly preferred embodiments, the present methods are directed to the treatment of inflammatory bowel disease wherein the compound of the invention is used alone or in combination with a second therapeutic agent selected from sulfasalazine and analogs (e.g., olsalazine), mesalamine, corticosteroids (e.g., prednisone, prednisolone) and analogs (e.g., budesonide), azathioprine, 6-mercaptopurine, cyclosporine A, methotrexate, infliximab and an IL-1 inhibitor.

In other particularly preferred embodiments, the present methods are directed to the treatment of multiple sclerosis using a compound of the invention either

alone or in combination with a second therapeutic agent selected from interferon β -1 β , interferon β -1 α , azathioprine, glatiramer acetate, a glucocorticoid (*e.g.*, prednisolone) and cyclophosphamide.

5 Methods of Evaluating Putative IRAK Modulators

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10 In yet another aspect, the present invention includes methods to evaluate putative specific agonists or antagonists of IRAK function. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the function of the IRAK. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to IRAK, *e.g.*, by competitive inhibition. The compounds of the instant invention are also
15 useful for the evaluation of putative specific modulators of IRAK.

The following examples are offered by way of illustration and not by way of limitation.

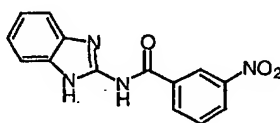
20

EXAMPLES

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^1H -NMR spectra
25 were recorded on a Bruker 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz), number of protons. Electron Ionization (EI) mass spectra were recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative
30 abundance of each ion (in parentheses). In tables, a single m/e value is reported for the $M+H$ (or, as noted, $M-H$) ion containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard 1100 MSD electrospray

mass spectrometer using the HP1 100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1 mg/mL and 1 microliter (μL) was infused with the delivery solvent into the mass spectrometer, which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using 1:1 acetonitrile/water with 1% acetic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2mM NH_4OAc in acetonitrile/water as delivery solvent.

Example 1

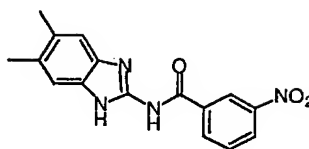


1

Synthesis of 3-nitro-*N*-(1*H*-benzimidazol-2-yl)-benzamide (1). A 200

mL flask was charged with 2.25 g 3-nitrobenzoic acid (13.46 mmol, 1.0 equiv), 3.59 g 2-aminobenzimidazole (26.92 mmol, 2.0 equiv), 5.63 g *O*-benzotriazol-1-yl-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HBTU, 14.81 mmol, 1.10 equiv), and 1-hydroxybenzotriazole hydrate (HOBT, 14.13 mmol, 1.05 equiv). The flask was then charged with 40 mL DMF, stirring was initiated (magnetic stirrer) and 1.71 mL *N*-methylmorpholine (NMM, 15.48 mmol, 1.15 equiv) was added in one portion to the suspension. After 6 h, the suspension was diluted with 200 mL of a 10% citric acid solution. After stirring an additional 30 min, the suspension was filtered and the resulting solid was washed (2 x H_2O , then 2 x sat. NaHCO_3). The solid was then triturated with EtOAc (30 mL), filtered, and dried under reduced pressure to give 3.16 g of the product as a tan solid (11.2 mmol). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 12.60 (broad s, 2 H), 8.96 (t, $J = 2.1$ Hz, 1 H), 8.55 (d, $J = 7.8$ Hz, 1 H), 8.38 (m, 1 H), 7.78 (t, $J = 7.9$ Hz, 1 H), 7.43 (dd, $J = 3.2, 5.9$ Hz, 2 H), 7.18 (dd, $J = 3.2, 5.9$ Hz, 2 H); MS: ESI(-) m/z 281.1 (M - H).

Example 2

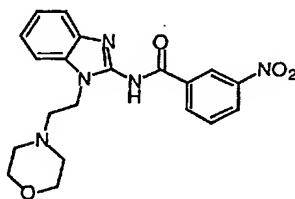


2

Synthesis of 3-nitro-*N*-(5,6-dimethyl-1*H*-benzoimidazol-2-yl)-

benzamide (2). Using the same method as example 1, but substituting 2-amino-5,6-dimethylbenzimidazole for 2-aminobenzimidazole the following was prepared: 3-Nitro-*N*-(5,6-dimethyl-1*H*-benzoimidazol-2-yl)-benzamide: ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.40 (broad s, 2 H), 8.96 (s, 1 H), 8.54 (d, $J = 7.8$ Hz, 1 H), 8.37 (dd, $J = 2.3, 8.1$ Hz, 1 H), 7.77 (t, $J = 8.0$ Hz, 1 H), 7.21 (s, 2 H), 2.28 (s, 6 H).

Example 3



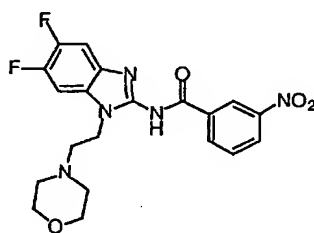
3

Synthesis of 3-nitro-*N*-(1-(2-morpholin-4-yl-ethyl)-1*H*-benzoimidazol-

2-yl)-benzamide (3). To a suspension of 3-nitro-*N*-(1*H*-benzoimidazol-2-yl)-benzamide prepared above in example 1 (150 mg, 0.532 mmol, 1.0 equiv) in 3 mL of 5:1 acetone:DMF was added 109 mg of 4-(2-chloroethyl)morpholine hydrochloride (0.585 mmol, 1.1 equiv) and 221 mg K_2CO_3 (1.60 mmol, 3.0 equiv). The resulting suspension was heated to 54 $^\circ\text{C}$ with stirring for 3 h. The suspension was then diluted with 10 mL sat. NaHCO_3 , and the acetone was removed under reduced pressure. The resulting suspension was then diluted with 20 mL CH_2Cl_2 , shaken until no solids remained, and passed through a 20 mm (40 mL) 3M Empore octadecyl (C18) cartridge to remove water.

The collected organics were then concentrated under reduced pressure. Purification by flash chromatography (SiO₂, 2-4% MeOH/CH₂Cl₂) gave 124 mg of the product as a tan solid (0.314 mmol). ¹H NMR (DMSO-d₆, 400 MHz) δ 12.85 (s, 1 H), 8.97 (s, 1 H), 8.61 (d, *J* = 7.6 Hz, 1 H), 8.38 (d, *J* = 7.5 Hz, 1 H), 7.79 (t, *J* = 8.0 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 2 H), 7.26 (m, 2 H), 4.42 (t, *J* = 5.9 Hz, 2 H), 3.49 (m, 4 H), 2.75 (t, *J* = 5.9 Hz, 2 H), 2.55 (m, 4 H).

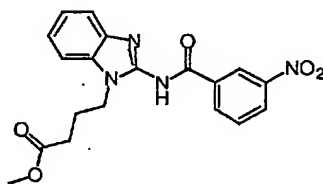
Example 4



4

Synthesis of 3-nitro-*N*-(1-(2-morpholin-4-yl-ethyl)-5,6-difluoro-1*H*-benzoimidazol-2-yl)-benzamide(4). Using the methods described in Examples 1 and 3 above, substituting 5,6-difluoro-2-aminobenzimidazole for 2-amino benzimidazole the following was prepared: 3-Nitro-*N*-(1-(2-morpholin-4-yl-ethyl)-5,6-difluoro-1*H*-benzoimidazol-2-yl)-benzamide: ¹H NMR (DMSO-d₆, 400 MHz) δ 12.90 (s, 1 H), 8.93 (s, 1 H), 8.59 (d, *J* = 7.7 Hz, 1 H), 8.38 (dd, *J* = 1.6, 8.1 Hz, 1 H), 7.87 (dd, *J* = 7.1, 10.6 Hz, 1 H), 7.78 (t, *J* = 7.9 Hz, 1 H), 7.52 (dd, *J* = 7.4, 10.1 Hz, 1 H), 4.38 (t, *J* = 6.3 Hz, 2 H), 3.44 (m, 4 H), 2.73 (m, 2 H), 2.53 (m, 4 H).

Example 5

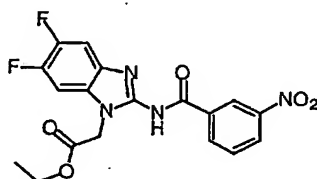


5

Synthesis of 3-nitro-*N*-(1-(3-carboxymethylpropyl)-1*H*-benzimidazol-2-yl)-benzamide (5). Using the methods described in examples 1 and 3, but substituting methyl 4-iodobutyrate for 4-(2-chloroethyl)morpholine hydrochloride the following was prepared: 3-Nitro-*N*-(1-(3-carboxymethylpropyl)-1*H*-benzimidazol-2-yl)-benzamide:

¹H NMR (DMSO-*d*₆, 400 MHz) δ 12.85 (s, 1 H), 8.93 (s, 1 H), 8.67 (d, *J* = 7.6 Hz, 1 H), 8.37 (dd, *J* = 2.4, 8.1 Hz, 1 H), 7.78 (t, *J* = 7.9 Hz, 1 H), 7.58 (d, *J* = 8.3 Hz, 2 H), 7.27 (m, 2 H), 4.35 (t, *J* = 6.7 Hz, 2 H), 3.34 (s, 3 H), 2.43 (t, *J* = 7.0 Hz, 2 H), 2.10 (m, 2 H); MS: ESI(-) *m/z* 381.1 (M - H).

Example 6



6

Synthesis of 3-nitro-*N*-(1-(ethyl acet-2-yl)-5,6-difluoro-1*H*-benzimidazol-2-yl)-benzamide (6). Using the methods described in examples 1 and 3 above, substituting 5,6-difluoro-2-aminobenzimidazole for 2-amino benzimidazole and ethyl 2-iodoacetate for 4-(2-chloroethyl)morpholine hydrochloride the following was prepared: 3-nitro-*N*-(1-(ethyl acet-2-yl)-5,6-difluoro-1*H*-benzimidazol-2-yl)-benzamide:

¹H NMR (DMSO-*d*₆, 400 MHz) δ 13.0 (s, 1 H), 8.86 (t, *J* = 2.1 Hz, 1 H), 8.56 (d, *J* = 7.7 Hz, 1 H), 8.38 (dd, *J* = 1.4, 8.1 Hz, 1 H), 7.86 (dd, *J* = 7.0, 10.5 Hz, 1 H), 7.76 (t, *J* = 8.0 Hz, 1 H), 7.51 (dd, *J* = 7.3, 10.0 Hz, 1 H), 5.13 (s, 2 H), 4.22 (m, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H).

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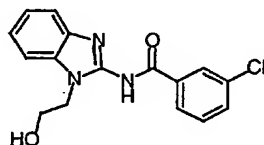


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ethyl-1*H*-benzoimidazol-2-yl)-benzamide: ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.60 (s, 1 H), 8.20 (d, J = 8.5 Hz, 2 H), 7.49 (dd, J = 4.6, 6.9 Hz, 2 H), 7.20 (m, 2 H), 6.99 (d, J = 8.5 Hz, 2 H), 4.27 (dd, J = 6.5, 13.5 Hz, 2 H), 3.84 (s, 3 H), 1.33 (t, J = 7.0 Hz, 3 H).

5

Example 9



9

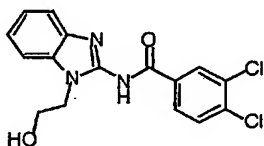
10

Synthesis of 3-chloro-*N*-(1-hydroxyethyl-1*H*-benzoimidazol-2-yl)-benzamide (9). Using the methods described in examples 1 and 3 above, substituting 3-chlorobenzoic acid for 3-nitrobenzoic acid, and 2-iodoethanol for 4-(2-chloroethyl)morpholine hydrochloride the following was prepared: 3-Chloro-*N*-(1-hydroxyethyl-1*H*-benzoimidazol-2-yl)-benzamide: ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.80 (s, 1 H), 8.18 (m, 2 H), 7.60-7.48 (m, 4 H), 7.23 (m, 2 H), 4.97 (t, J = 5.5 Hz, 1 H), 4.32 (t, J = 5.5 Hz, 2 H), 3.82 (dd, J = 5.3, 10.7 Hz, 2 H).

15

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Example 10



10

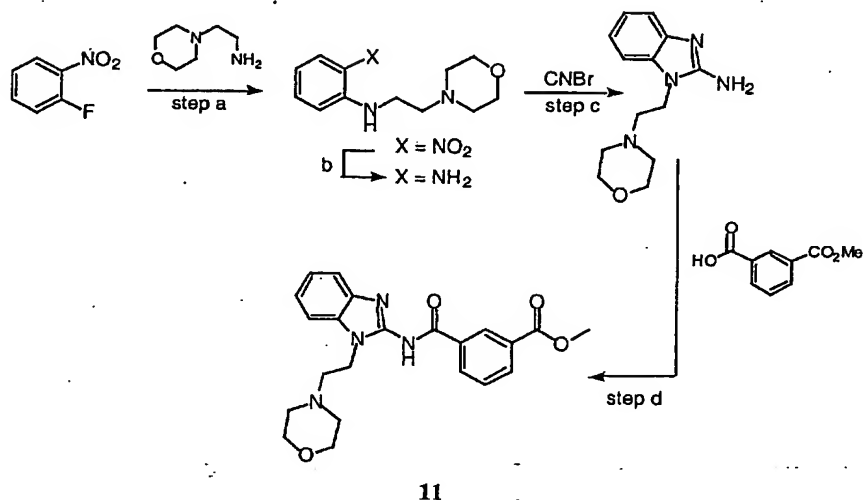
20

Synthesis of 3,4-dichloro-*N*-(1-hydroxyethyl-1*H*-benzoimidazol-2-yl)-benzamide (10). Using the methods described in examples 1 and 3 above, substituting 3,4-dichlorobenzoic acid for 3-nitrobenzoic acid, and 2-iodoethanol for 4-(2-chloroethyl)morpholine hydrochloride the following was prepared: 3,4-Dichloro-*N*-(1-hydroxyethyl-1*H*-benzoimidazol-2-yl)-benzamide: ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.80 (s, 1 H), 8.30 (d, J = 8.3 Hz, 1 H), 8.17 (dd, J = 1.9, 8.3 Hz, 1 H), 7.75 (d, J = 8.3

25

Hz, 1 H), 7.53 (m, 2 H), 7.22 (m, 2 H), 4.94 (t, $J = 5.6$ Hz, 1 H), 4.31 (t, $J = 5.5$ Hz, 2 H), 3.81 (dd, $J = 5.4, 10.9$ Hz, 2 H).

Example 11



Synthesis of 3-carboxymethyl-N-(1-(2-morpholin-4-yl-ethyl)-1H-benzimidazol-2-yl)-benzamide (11).

(a) 2-(4-(2-Aminoethyl)morpholine)nitrobenzene: To a 25 mL flask containing 2.0 mL 2-fluoronitrobenzene (19.0 mmol, 1.0 equiv) was carefully added 2.48 mL 4-(2-aminoethyl)morpholine (19.0 mmol, 1.0 equiv) over a period of 15 min (*caution, exothermic reaction*). The reaction was allowed to stir for 12 h at which time it was diluted with sat. NaHCO_3 . The solution was then extracted (3 x CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2 , 0-5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) gave the product 2-(4-(2-aminoethyl)morpholine)nitrobenzene as a yellow oil 3.69 g (14.7 mmol).

(b) 2-(4-(2-Aminoethyl)morpholine)aniline: A 200 mL flask was charged with 1.0 g of palladium on carbon (5 wt%), and 5 mL EtOH under N_2 . 3.7 g 2-(4-(2-Aminoethyl)morpholine)nitrobenzene (14.7 mmol, 1.0 equiv) was dissolved in 20 mL EtOH, and the solution was added to the catalyst suspension, followed by the addition of 7 mL cyclohexene. The flask was equipped with a reflux condenser, and heated to 83 °C.

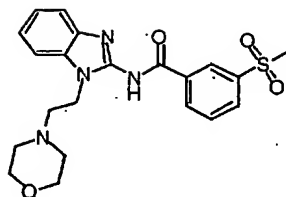
After stirring for 1 h, the suspension was removed from the heating bath and allowed to cool to rt. The suspension was then filtered through a pad of celite to remove the catalyst, and the celite pad was washed 6 x EtOH. The combined organics were concentrated under reduced pressure to give the product 2-(4-(2-aminoethyl)morpholine)aniline as a black viscous oil which was sufficiently pure to continue to the next step (3.96 g, quant.).

(c) 1-(2-Morpholin-4-yl-ethyl)-2-aminobenzimidazole: A 250 mL flask was charged with 40 mL H₂O followed by the addition of 3.94 mL of a 5.0 M solution of cyanogen bromide in CH₃CN (19.7 mmol, 1.1 equiv). The 2-(4-(2-aminoethyl)morpholine)aniline prepared above (3.96 g, ~17.92 mmol, 1.0 equiv) was dissolved in 40 mL MeOH, and was introduced via addition funnel over a period of 1 h to the cyanogen bromide solution. After stirring for 24 h the solution was concentrated under reduced pressure to remove MeOH, and the resulting acidic aqueous solution was washed 2 x EtOAc. The EtOAc fractions were back extracted 1 x H₂O, and the combined aqueous solutions were neutralized with sat. NaHCO₃. The slightly basic aqueous solution was then extracted 4 x EtOAc. The organics from the basic extraction were then washed (1 x brine), dried (MgSO₄), and concentrated under reduced pressure to give the crude product 1-(2-morpholin-4-yl-ethyl)-2-aminobenzimidazole as a dark brown solid.

(d) 3-Carboxymethyl-*N*-(1-(2-morpholin-4-yl-ethyl)-1*H*-benzoimidazol-2-yl)-benzamide: A portion of the product 1-(2-morpholin-4-yl-ethyl)-2-aminobenzimidazole obtained above (100 mg, 0.406 mmol, 1.0 equiv) was combined in a flask with 169 mg *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU, 0.447 mmol, 1.1 equiv), 73.2 mg 3-carboxymethylbenzoic acid (0.406 mmol, 1.0 equiv) and 58 mg 1-hydroxybenzotriazole hydrate (HOBT, 0.426 mmol, 1.05 equiv) followed by the addition of 2 mL DMF and 51 μ L *N*-methylmorpholine (NMM, 0.467 mmol, 1.15 equiv). The solution was allowed to stir for 24 h followed by dilution with 30 mL sat. NaHCO₃. The resulting solution was extracted (1 x EtOAc), dried (Na₂SO₄), and concentrated under reduced pressure. Purification by flash chromatography (SiO₂, 2-4% MeOH/CH₂Cl₂) gave the product as a tan solid (53 mg, 0.130 mmol). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 12.8 (s, 1 H), 8.82 (s, 1 H), 8.44 (m, 1 H), 8.08 (m, 1 H), 7.64 (m, 1 H), 7.55 (m, 2 H), 7.25 (m, 2 H), 4.39 (m, 2 H), 3.85 (s, 3 H), 3.48 (m, 4 H), 2.71 (m, 2 H), 2.50 (m, 4 H).

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Example 12

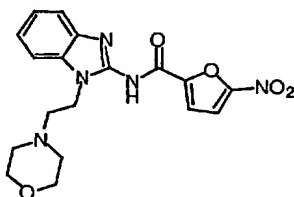


12

5 **Synthesis of 3-methanesulfonyl-N-(1-(2-morpholin-4-yl-ethyl)-1H-benzoimidazol-2-yl)-benzamide (12).** Using the methods described above in example 11 the following compounds were prepared substituting the appropriate carboxylic acid for 3-carboxymethylbenzoic acid in step (d):

10 **3-Methanesulfonyl-N-(1-(2-morpholin-4-yl-ethyl)-1H-benzoimidazol-2-yl)-benzamide** from 1-(2-morpholin-4-yl-ethyl)-2-aminobenzimidazole and 3-methanesulfonylbenzoic acid: ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.81 (s, 1 H), 8.72 (s, 1 H), 8.51 (d, $J = 7.7$ Hz, 1 H), 8.09 (d, $J = 7.8$ Hz, 1 H), 7.77 (t, $J = 7.8$ Hz, 1 H), 7.57 (m, 2 H), 7.24 (m, 2 H), 4.42 (t, $J = 6.4$ Hz, 2 H), 3.47 (m, 4 H), 3.33 (s, 3 H), 2.70 (m, 2 H), 2.49 (m, 4 H).

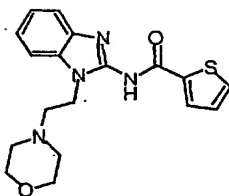
Example 13



13

20 **Synthesis of 5-nitro-N-(1-(2-morpholin-4-yl-ethyl)-1H-benzoimidazol-2-yl)-2-furamide (13).** 5-Nitro-N-(1-(2-morpholin-4-yl-ethyl)-1H-benzoimidazol-2-yl)-2-furamide from 1-(2-morpholin-4-yl-ethyl)-2-aminobenzimidazole and 5-nitro-2-furoic acid: ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.70 (s, 1 H), 7.73 (m, 1 H), 7.57 (m, 2 H), 7.35 (m, 1 H), 7.28 (m, 2 H), 4.38 (m, 2 H), 3.43 (m, 4 H), 2.70 (m, 2 H), 2.50 (m, 4 H).

Example 14



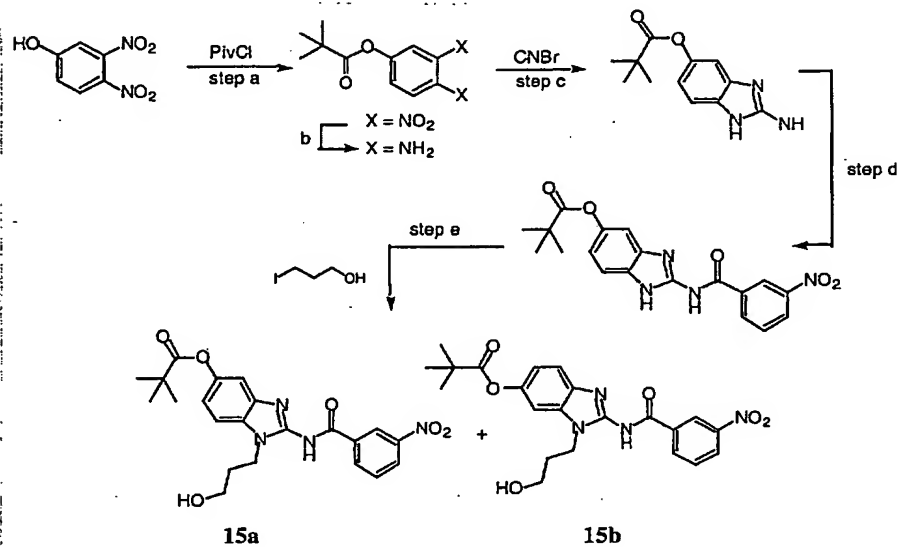
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Synthesis of *N*-(1-(2-morpholin-4-yl-ethyl)-1*H*-benzoimidazol-2-yl)-2-thiophenecarboxamide (14). *N*-(1-(2-Morpholin-4-yl-ethyl)-1*H*-benzoimidazol-2-yl)-2-thiophenecarboxamide from 1-(2-morpholin-4-yl-ethyl)-2-aminobenzimidazole and thiophene-2-carboxylic acid: ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.55 (s, 1 H), 7.69 (dd, $J = 3.4, 7.7$ Hz, 2 H), 7.52 (m, 2 H), 7.22 (m, 2 H), 7.12 (t, $J = 4.8$ Hz, 1 H), 4.33 (t, $J = 6.1$ Hz, 2 H), 3.45 (m, 4 H), 2.71 (m, 2 H), 2.49 (m, 4 H).

10

Example 15



Synthesis of 3-nitro-*N*-(1-hydroxypropyl-5-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide (15a) and 3-Nitro-*N*-(1-hydroxypropyl-6-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide (15b). This example

illustrates the synthesis of 3-nitro-*N*-(1-hydroxypropyl-5-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide and 3-Nitro-*N*-(1-hydroxypropyl-6-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide as a mixture of the two isomers:

(a) 4-(2',2'-Dimethylpropionyl)-1,2-dinitrobenzene: A 1L flask was charged with 10 g (54.3 mmol, 1.0 equiv) 3,4-dinitrophenol and 300 mL CH₂Cl₂. The resulting solution was cooled in an ice bath to 0 °C followed by the addition of 9.84 mL triethylamine (70.6 mmol, 1.3 equiv) and 7.35 mL pivoyl chloride (59.7 mmol, 1.1 equiv). After stirring for 15 min the solution was diluted with sat. NaHCO₃ and extracted (2 x CH₂Cl₂). The CH₂Cl₂ solution was then dried (Na₂SO₄) and concentrated under reduced pressure to give the 4-(2',2'-dimethylpropionyl)-1,2-dinitrobenzene product as a light golden oil which was used directly in the next step.

(b) 4-(2',2'-dimethylpropionyl)-1,2-aminobenzene: A 250 mL flask which had been purged under nitrogen was charged with 2 g 5% wt palladium on carbon and 20 mL EtOH. The starting material (4-(2',2'-dimethylpropionyl)-1,2-dinitrobenzene produced in step a above, ~54 mmol) was dissolved in 140 mL EtOH and added to the flask, followed by the addition of 46 mL cyclohexene. The flask was then equipped with a reflux condenser and heated to 80 °C. After heating for 24 h the hot suspension was filtered through celite, and the celite pad was washed (4 x EtOH). The combined EtOH solutions were concentrated under reduced pressure to give 10.71 g of the product 4-(2',2'-dimethylpropionyl)-1,2-aminobenzene which was taken on to the next step without further purification (51.4 mmol).

(c) 2-Amino-5-(2',2'-dimethylpropionyl)benzimidazole: To a flask containing 60 mL H₂O was added 11.32 mL of a 5.0 M solution of cyanogen bromide in CH₃CN followed by the addition of 10.71 g 4-(2',2'-dimethylpropionyl)-1,2-aminobenzene (51.5 mmol, prepared above in step b, 1.0 equiv) in 60 mL EtOH over 30 min via addition funnel. After stirring for 20 h the solution was concentrated under reduced pressure to remove the EtOH. The resulting aqueous solution was washed (2 x EtOAc), and the EtOAc fractions were back extracted 2 x H₂O. The combined aqueous layers were made basic with sat. NaHCO₃, and then extracted (3 x EtOAc). The organic layer was then washed (1 x brine), dried (MgSO₄), and concentrated under reduced pressure to give the product benzimidazole as a brown solid (8.59 g, 36.8 mmol): ¹H

NMR (DMSO- d_6 , 400 MHz) δ 7.04 (d, J = 8.3 Hz, 1 H), 6.79 (d, J = 2.2 Hz, 1 H), 6.53 (dd, J = 2.2, 8.3 Hz, 1 H), 6.31 (broad s, 2 H), 1.28 (s, 9 H).

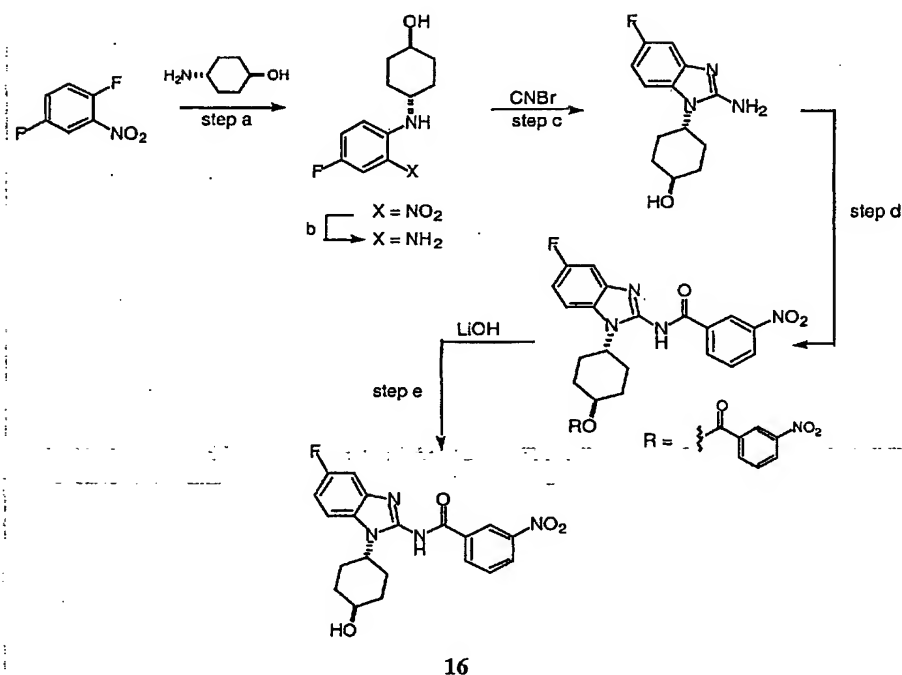
(d) 3-Nitro-*N*-(5-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide: A dry flask was charged with 2.56 g 3-nitrobenzoic acid (15.3 mmol, 1.0 equiv), 4.65 g 2-amino-5-(2',2'-dimethylpropionyl)benzimidazole (prepared above in step c, 19.9 mmol, 1.3 equiv), 2.18 g 1-hydroxybenzotriazole hydrate (HOBT, 16.1 mmol, 1.05 equiv), and 6.39 g *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU, 16.8 mmol, 1.10 equiv). 45 mL DMF was then added followed by 1.94 mL *N*-methylmorpholine (NMM, 17.6 mmol, 1.15 equiv). The resulting slurry was allowed to stir for 20 h, and was then diluted with a 10% citric acid solution and extracted (3 x EtOAc). The organics were washed (1 x 10% citric acid, 2 x sat. NaHCO₃, 1 x brine), dried (Na₂SO₄), and concentrated under reduced pressure. The resulting solid was triturated from MeOH, filtered, washed (3 x MeOH), and dried under reduced pressure to give the product as a tan solid (4.87 g, 12.7 mmol): ¹H NMR (DMSO- d_6 , 400 MHz) δ 12.60 (broad s, 2 H), 8.96 (t, J = 1.9 Hz, 1 H), 8.55 (d, J = 7.8 Hz, 1 H), 8.41 (dd, J = 1.5, 8.2 Hz, 1 H), 7.81 (t, J = 7.9 Hz, 1 H), 7.45 (d, J = 8.6 Hz, 1 H), 7.16 (d, J = 2.2 Hz, 1 H), 6.91 (dd, J = 2.2, 8.5 Hz, 1 H), 1.30 (s, 9 H).

(e) 3-Nitro-*N*-(1-hydroxypropyl-5-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide and 3-Nitro-*N*-(1-hydroxypropyl-5-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide: 2.24 g of 3-Nitro-*N*-(5-(2',2'-dimethylpropionyl)-1*H*-benzoimidazol-2-yl)-benzamide (prepared above in step d, 5.86 mmol, 1.0 equiv) was combined in a flask with 2 mL 3-iodopropanol (20.9 mmol, 3.6 equiv), 2 g K₂CO₃ (14.5 mmol, 2.5 equiv), and 30 mL of a 5:1 solution of acetone/DMF. The suspension was heated to 55 °C for 25 min, and then poured into a solution of sat. NaHCO₃. The acetone was removed under reduced pressure, and the aqueous solution was then extracted (4 x CH₂Cl₂), washed (2 x H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. The resulting solid was triturated with MeOH, filtered, washed (3 x MeOH), and dried under reduced pressure to give the product as a tan solid 953 mg (2.17 mmol): ¹H NMR (DMSO- d_6 , 400 MHz, mixture of isomers) δ 12.90 (s, 1 H), 8.95 (s, 1 H), 8.66 (d, J = 7.7 Hz, 1 H), 8.39 (dd, J = 1.5, 8.1 Hz, 1 H), 7.78 (t, J = 7.9 Hz, 1 H), 7.56 (dd, J = 8.7, 13.9 Hz, 1 H), 7.40 (d, J = 2.1 Hz, 0.5 H), 7.25 (d, J = 2.2 Hz, 0.5 H), 7.03 (dd, J = 2.2, 8.6 Hz, 0.5 H), 6.98 (dd, J = 2.1, 8.5 Hz, 0.5 H), 4.65 (broad s, 1 H),

4.35 (m, 2 H), 3.50 (m, 2 H), 1.98 (m, 2 H), 1.32 (s, 9 H). Anal. calcd for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.69; H, 5.59; N, 12.63.

Example 16

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10 **Synthesis of 3-nitro-N-(1-(*trans*-4-cyclohexanol-1-yl)-5-fluoro-1H-benzimidazol-2-yl)-benzamide (16).**

(a) 2-(*trans*-4-Cyclohexanol-1-yl)-4-fluoronitrobenzene: A flask was charged with 2.35 mL 2,5-difluoronitrobenzene (21.7 mmol, 1.0 equiv), followed by the slow addition of 2.5 g *trans*-1,4-cyclohexanolamine (21.7 mmol, 1.0 equiv). The slurry was then diluted with 3 mL Et₂O, and allowed to stir. After stirring for 12 h, the bright orange slurry was diluted with sat. NaHCO₃, extracted (3 x CH₂Cl₂), washed (1 x H₂O), dried (Na₂SO₄), and concentrated under reduced pressure. Purification by flash chromatography (SiO₂, 0-5% MeOH/CH₂Cl₂) gave 1.975 g of product 2-(*trans*-4-cyclohexanol-1-yl)-4-fluoronitrobenzene as a yellow solid (7.77 mmol).

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(b) 2-(*trans*-4-Cyclohexanol-1-yl)-4-fluoroaniline: A nitrogen purged flask was charged with 1 g palladium on carbon (5 wt %), which was covered with 10 mL EtOH. 2-(*trans*-4-Cyclohexanol-1-yl)-4-fluoronitrobenzene (prepared above in step a, 1.975 g, 7.77 mmol) was dissolved in 30 mL EtOH, and the solution was added to the catalyst suspension followed by the addition of 12 mL cyclohexene. The flask was equipped with a reflux condenser, and then placed into a preheated 80 °C bath. After stirring for 2 h, the solution was hot filtered through a plug of celite. The celite plug was washed (3 x EtOH), and the combined EtOH fraction were concentrated under reduced pressure to give 1.58 g of the product as a tan solid (7.05 mmol).

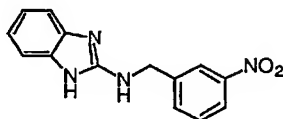
(c) 2-Amino-1-(*trans*-4-cyclohexanol-1-yl)-5-fluorobenzimidazole: A 250 mL flask was charged with 30 mL H₂O and 1.55 mL (7.75 mmol, 1.1 equiv) of a 5.0M solution of cyanogen bromide in CH₃CN. 2-(*trans*-4-Cyclohexanol-1-yl)-4-fluoroaniline (prepared above in step b, 1.58 g, 7.05 mmol, 1.0 equiv) was dissolved in 20 mL MeOH, followed by addition over a period of 20 min via addition funnel to the cyanogen bromide solution. After stirring for 16 h, the solution was concentrated under reduced pressure to remove MeOH. The resulting aqueous solution was washed (2 x EtOAc), and the EtOAc wash was back extracted 1 x H₂O. The organics were discarded, and the aqueous solution was made basic with sat. NaHCO₃. The slurry was then extracted (4 x EtOAc), washed (1 x brine), dried (MgSO₄), and concentrated under reduced pressure to give 1.31 g of the product 2-amino-1-(*trans*-4-cyclohexanol-1-yl)-5-fluorobenzimidazole as a tan solid (5.26 mmol). ¹H NMR (DMSO-d₆, 400 MHz) δ 7.27 (dd, *J* = 4.9, 8.7 Hz, 1 H), 6.86 (dd, *J* = 2.5, 10.1 Hz, 1 H), 6.61 (m, 1 H), 6.46 (s, 2 H), 4.65 (s, 1 H), 4.15 (m, 1 H), 3.61 (m, 1 H), 2.15 (m, 2 H), 1.93 (m, 2 H), 1.68 (, 2 H), 1.40 (m, 2 H); MS: ESI(+) *m/z* 250.2 (M + H⁺).

(d) 3-Nitro-*N*-(1-(*trans*-4-(3-nitrobenzoyl)cyclohexane-1-yl)-5-fluoro-1*H*-benzoimidazol-2-yl)-benzamide: 2-Amino-1-(*trans*-4-cyclohexanol-1-yl)-5-fluorobenzimidazole (879 mg, 3.525 mmol, 1.0 equiv, prepared above in step c) was combined in a flask with 3.09 g *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU, 8.15 mmol, 2.31 equiv), 1.24 g 3-nitrobenzoic acid (7.42 mmol, 2.1 equiv), and 1.05 g 1-hydroxybenzotriazole hydrate (HOBT, 7.77 mmol, 2.2 equiv). 15 mL DMF was added, followed by 935 μL *N*-methylmorpholine (NMM, 8.50 mmol, 2.41 equiv). The resulting slurry was allowed to stir for 24 h, followed by the addition of a 10% solution of citric acid. The resulting slurry was extracted (3 x EtOAc),

washed (1 x 10% citric acid, 2 x sat. NaHCO_3 , 1 x brine), dried (MgSO_4), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2 , 0-5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) gave the product as a yellow solid 1.16 g (2.12 mmol). ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.95 (s, 1 H), 8.95 (t, $J = 1.9$ Hz, 1 H), 8.69 (d, $J = 9.0$ Hz, 1 H), 8.67 (t, $J = 1.7$ Hz, 1 H), 8.53 (dd, $J = 2.3, 8.2$ Hz, 1 H), 8.43 (d, $J = 7.8$ Hz, 1 H), 8.39 (dd, $J = 1.5, 8.1$ Hz, 1 H), 7.92-7.79 (m, 3 H), 7.40 (dd, $J = 2.6, 8.8$ Hz, 1 H), 7.13 (ddd, $J = 2.6, 9.1, 9.5$ Hz, 1 H), 5.30 (m, 1 H), 5.0 (m, 1 H), 2.65 (m, 2 H), 2.28 (m, 2 H), 1.90 (m, 4 H); MS: ESI(-) m/z 546.2 (M - H).

(e) 3-Nitro-*N*-(1-(*trans*-4-cyclohexanol-1-yl)-5-fluoro-1*H*-benzimidazol-2-yl)-benzamide: The ester prepared above in step d (100 mg, 0.183 mmol) was combined with MeOH (10 mL), H_2O (3 mL), and THF (3 mL) followed by the addition of 100 mg LiOH. The suspension was heated to 53 $^\circ\text{C}$ for 2 h, over which time the suspension slowly went into solution. At the end of 2 h, the solution was concentrated under reduced pressure, diluted with sat. NaHCO_3 , and extracted 3 x CH_2Cl_2 . The solution was washed (2 x sat. NaHCO_3), dried (Na_2SO_4), and concentrated under reduced pressure to give the product as a yellow solid 73 mg (0.183 mmol, quant.). ^1H NMR (DMSO- d_6 , 400 MHz) δ 12.97 (s, 1 H), 8.98 (s, 1 H), 8.60 (d, $J = 7.6$ Hz, 1 H), 8.38 (dd, $J = 2.0, 8.1$ Hz, 1 H), 7.79 (t, $J = 7.9$ Hz, 1 H), 7.94 (dd, $J = 4.5, 8.8$ Hz, 1 H), 7.35 (dd, $J = 2.4, 8.7$ Hz, 1 H), 7.11 (m, 1 H), 4.77 (m, 2 H), 3.72 (m, 1 H), 2.01 (m, 2 H), 1.80 (m, 2 H), 1.49 (m, 2 H); Anal. calcd for $\text{C}_{20}\text{H}_{19}\text{FN}_4\text{O}_4$: C, 60.30; H, 4.81; N, 14.06. Found: C, 60.11; H, 4.88; N, 13.97.

Example 17



17

Synthesis of 2-benzylaminobenzimidazole (17). A 100 mL flask was charged with 1.0 g 2-aminobenzimidazole (7.51 mmol, 1.0 equiv), 1.13 g 3-nitrobenzaldehyde (7.51 mmol, 1.0 equiv), and 25 mL toluene. The flask was equipped with a Dean-Stark trap and reflux condenser and placed in a 110 $^\circ\text{C}$ bath. The solution was refluxed for 15.5 h, followed by the addition of 3 mL MeOH and 3 mL

diisopropylethylamine. After refluxing an additional 29 h, the flask was removed, and the volatiles were removed under reduced pressure at 70 °C. The remaining material was diluted with 50 mL MeOH, and cooled to 0 °C followed by the addition of 426 mg (11.27 mmol, 1.5 equiv) NaBH₄. After stirring for 3 h, the solution was concentrated under reduced pressure, and the residue was applied directly to a SiO₂ column (preflushed with 10% MeOH/CH₂Cl₂). The column was eluted with 10% MeOH/CH₂Cl₂ to give the product as an orange solid 320 mg (1.19 mmol). ¹H NMR (DMSO-d₆, 400 MHz) δ 11.0 (broad s, 1 H), 8.25 (s, 1 H), 8.11 (d, *J* = 8.2 Hz, 1 H), 7.85 (d, *J* = 7.5 Hz, 1 H), 7.62 (t, *J* = 8.0 Hz, 1 H), 7.34 (m, 1 H), 7.13 (t, *J* = 3.7 Hz, 2 H), 6.86 (s, 2 H), 4.64 (d, *J* = 5.8 Hz, 2 H); MS: ESI(+) *m/z* 269.2 (M + H⁺).

Example 18

Enzymatic inhibition assay. This example provides a method that is useful for evaluating test compounds for inhibition of IRAK-1 or IRAK-4 kinase activity.

Protocol

96-well polystyrene microtiter plates were coated with neutravidin for IRAK-1 or streptavidin for IRAK-4 (10 mg/mL in PBS, overnight at 4 °C). The coating solution was removed and in 80 μL/well a kinase reaction mixture was added (for IRAK-1: 20 mM Tris-HCl, pH 7.5, 10 mM MgCl₂, 2 mM EGTA, 1 mM NaF, 0.5 mM benzamidine, 1 mM DTT, 3 μM ATP, 1mM of biotinylated substrate peptide bio-ARFSRFAGSSPSQSSMVAR, sequence derived from IRAK-1; for IRAK-4: 20 mM Tris-HCl, pH 7.5, 10 mM MgCl₂, 2 mM EGTA, 1 mM NaF, 0.5 mM benzamidine, 1 mM DTT, 10% glycerol, 10 μM ATP, 1mM of biotinylated substrate peptide bio-RRRVTSPARRS, sequence derived from GFAP).

At 10 μL/well in DMSO test compounds were added covering a final concentration range from 1nM to 30mM. Recombinant, full-length IRAK-1 or IRAK-4 enzyme (baculovirus expression system) was added in 10 μL buffer containing Tris-HCl pH 7.5 20 mM, EGTA 2 mM, benzamidine 0.5 mM, DTT 1 mM, MgCl₂ 10 mM and glycerol 10% (IRAK-4 only) to initiate the kinase reaction. The reaction mixture was incubated at room temperature for 60 min on a shaker. During this incubation the substrate peptide is being phosphorylated by the kinase and gets captured onto the surface

of the wells by neutravidin or streptavidin, respectively. The plate was washed 3x with 150 μ L distilled water to terminate the reaction and remove components of the reaction mixture. A conventional chemiluminescent ELISA detection technique was initiated by adding 100 μ L/well primary antibody (monoclonal antibody YC10, generated to recognize the phosphorylated epitope in the substrate peptide; used at 1:20,000 dilution for IRAK-1 and 1:10,000 dilution for IRAK-4) premixed with horseradish peroxidase (HRP) conjugated anti-mouse secondary antibody (commercially available from several sources; used at 1:10,000 dilution) in PBS containing 2% BSA. The solution was incubated at room temperature for 40 min on a shaker, then washed 3x with 150 μ L of water. 100 μ L/well 10x diluted SuperSignal HRP substrate (from Pierce) was added and after 5 min incubation the chemiluminescent signal was captured by a Labsystems LuminoSkan luminometer. The point of 50% inhibition of IRAK-1 or IRAK-4 enzyme activity (IC_{50}) was determined (see Table 1).

Table 1. IC_{50} values (μ M) for exemplary compounds of the invention.

Compound	IRAK-1	IRAK-4
1	++	++
2	+	++
3	++	++
4	++	++
5	++	++
6	+	++
7a	++	++
8	+	+
9	++	++
10	+	++
11	++	++
12	++	++
13	++	++
14	+	+
15a	++	++
16	++	++
17	+	+

Compound	IRAK-1	IRAK-4
19	+	+
20	++	++
21	+	ND
22	++	++
23	++	++
24	++	++
25	++	++
26	++	++
27	++	++
28	++	++
29	++	++
30	++	++
31	++	++
32	++	++

+- indicates $10 \mu\text{M} < \text{IC}_{50} \leq 30 \mu\text{M}$

++ indicates $\text{IC}_{50} \leq 10 \mu\text{M}$

ND indicates IC_{50} not determined

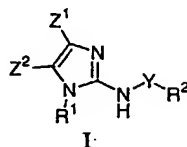
5 Sequences

IRAK-1 has a N-terminal Flag tag for purification. IRAK-4 has a N-terminal His Tag. An amino acid spacer is between Tag and the kinase.

10 All publications and patent applications cited in this specification are
 herein incorporated by reference as if each individual publication or patent application
 were specifically and individually indicated to be incorporated by reference. Although
 the foregoing invention has been described in some detail by way of illustration and
 example for purposes of clarity of understanding, it will be readily apparent to those of
 15 ordinary skill in the art in light of the teachings of this invention that certain changes and
 modifications may be made thereto without departing from the spirit or scope of the
 appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



or a pharmaceutically acceptable salt or prodrug thereof, wherein

R^1 is selected from the group consisting of H, (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl and heteroaryl;

R^2 is selected from the group consisting of (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, perfluoro(C₁-C₄)alkyl, aryl and heteroaryl;

Y is selected from the group consisting of C(O), S(O)_m, S(O)₂NR', C(O)NR', CR³R⁴, C(NR'), C(=CR³R⁴), CR³(OR') and CR³(NR'R''), wherein the subscript m is an integer selected from 1 to 2;

Z^1 and Z^2 are independently selected from the group consisting of H, halogen, CN, CO₂R', CONR'R'', (C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, perfluoro(C₁-C₄)alkyl, aryl, heteroaryl, NR'R'' and OR', or Z^1 and Z^2 may be combined to form an additional fused 5-, 6-, 7- or 8-membered cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring;

R^3 and R^4 are independently selected from the group consisting of H, CN, CO₂R', CONR'R'', (C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl, heteroaryl, NR'R'' and OR'; and

R' and R'' are independently selected from the group consisting of H, (C₁-C₄)alkyl, hetero(C₁-C₄)alkyl, aryl and aryl(C₁-C₄)alkyl;

alternatively, when R' and R'' are attached to nitrogen, R' and R'' may be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring; and

alternatively, when Y is CR³R⁴, C(NR'), C(=CR³R⁴), CR³(OR') or CR³(NR'R''), R^3 , R^4 or R' may be combined with R^2 to form a 5-, 6-, 7- or 8-membered ring containing from 0 to 3 heteroatoms selected from the group consisting of O, N, Si and S.

2. The compound of Claim 1, wherein Z^1 and Z^2 are combined to form an additional fused 6-membered ring.

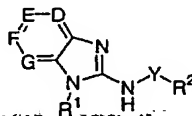
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- 1 3. The compound of Claim 1, wherein Z^1 and Z^2 are combined to
2 form an additional fused aryl, cycloalkyl or heterocycloalkyl ring.
- 1 4. The compound of Claim 1, wherein Z^1 and Z^2 are combined to
2 form an additional fused aryl ring.
- 1 5. The compound of Claim 4, wherein said aryl ring is a benzene ring.
- 1 6. The compound of Claim 1, wherein Z^1 and Z^2 are combined to
2 form an additional fused cycloalkyl ring.
- 1 7. The compound of Claim 6, wherein said cycloalkyl ring is a
2 cyclohexyl ring.
- 1 8. The compound of Claim 1, wherein Z^1 and Z^2 are combined to
2 form an additional fused heterocycloalkyl ring.
- 1 9. The compound of Claim 8, wherein said heterocycloalkyl ring is a
2 tetrahydropyranyl ring.
- 1 10. The compound of Claim 1, wherein Y is selected from the group
2 consisting of C(O), S(O)_m and CR³R⁴.
- 1 11. The compound of Claim 1, wherein Y is C(O).
- 1 12. The compound of Claim 1, wherein Y is S(O)_m, wherein the
2 subscript m is an integer selected from 1 to 2.
- 1 13. The compound of Claim 1, wherein Y is S(O)₂.
- 1 14. The compound of Claim 1, wherein Y is CR³R⁴.
- 1 15. The compound of Claim 1, wherein R¹ is H.
- 1 16. The compound of Claim 1, wherein R¹ is (C₁-C₈)alkyl or (C₁-
2 C₈)heteroalkyl.
- 1 17. The compound of Claim 1, wherein R¹ is substituted (C₁-C₈)alkyl
2 or substituted (C₁-C₈)heteroalkyl.

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- 1 18. The compound of Claim 1, wherein R¹ is (C₁-C₈)alkyl substituted
2 with OR', NR'R'', OC(O)R', CO₂R', CONR'R'', OC(O)NR'R'', NR''C(O)R' or
3 NR''CO₂R'.
- 1 19. The compound of Claim 1, wherein R¹ is (C₁-C₈)alkyl substituted
2 with OH.
- 1 20. The compound of Claim 1, wherein R¹ is cycloalkyl or
2 heterocycloalkyl.
- 1 21. The compound of Claim 1, wherein R¹ is substituted cycloalkyl or
2 substituted heterocycloalkyl.
- 1 22. The compound of Claim 1, wherein R¹ is cycloalkyl substituted
2 with OR', NR'R'', OC(O)R', CO₂R', CONR'R'', OC(O)NR'R'', NR''C(O)R' or
3 NR''CO₂R'.
- 1 23. The compound of Claim 1, wherein R¹ is cycloalkyl substituted
2 with OH.
- 1 24. The compound of Claim 1, wherein R¹ is cyclohexyl.
- 1 25. The compound of Claim 1, wherein R¹ is tetrahydropyranyl.
- 1 26. The compound of Claim 1, wherein R² is aryl or heteroaryl.
- 1 27. The compound of Claim 26, wherein said aryl is phenyl.
- 1 28. The compound of Claim 26, wherein said aryl is substituted
2 phenyl.
- 1 29. The compound of Claim 1, wherein R² is aryl or heteroaryl, Z¹ and
2 Z² are combined to form an additional fused aryl ring and Y is C(O).
- 1 30. The compound of Claim 1, wherein R¹ is substituted (C₁-C₈)alkyl
2 or substituted (C₁-C₈)heteroalkyl, R² is aryl, Z¹ and Z² are combined to form an additional
3 fused aryl ring and Y is C(O).

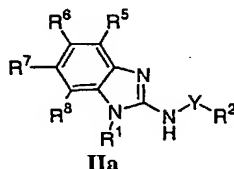
1 34. The compound of Claim 1, having the formula (II):



III

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35. The compound of Claim 1, having the formula (IIa):



wherein

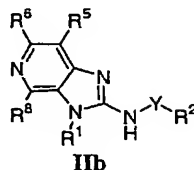
R^5 , R^6 , R^7 and R^8 are independently selected from the group consisting of H, halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl, aryl(C₁-C₄)alkyl, heteroaryl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR', and N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, alternatively, R^5 , R^6 , R^7 or R^8 may be combined with an adjacent R-group selected from the group consisting of R^1 , R^5 , R^6 , R^7 and R^8 to form an additional 5-, 6-, 7- or 8-membered ring.

36. The compound of Claim 35, wherein

R^1 is selected from the group consisting of (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl and heteroaryl; and

R^6 is selected from the group consisting of halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR', or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R^6 may be combined with R^5 or R^7 to form an additional 5-, 6-, 7- or 8-membered ring.

37. The compound of Claim 1, having the formula (IIb):



wherein

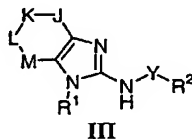
R^5 , R^6 and R^8 are independently selected from the group consisting of H, halogen, (C_1-C_4) alkyl, perfluoro (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl, aryl (C_1-C_4) alkyl, heteroaryl, CN, CO_2R' , $CONR'R''$, $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$, $S(O)_mNR'R''$, $S(O)_mR'$, and $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1 to 2, alternatively, R^6 may be combined with R^5 to form an additional 5-, 6-, 7- or 8-membered ring and R^8 may be combined with R^1 to form an additional 5-, 6-, 7- or 8-membered ring.

38. The compound of Claim 37 wherein

R^1 is selected from the group consisting of (C_1-C_8) alkyl, hetero (C_1-C_8) alkyl, fluoro (C_1-C_4) alkyl, cycloalkyl (C_1-C_8) alkyl, heterocyclo (C_1-C_8) alkyl, aryl, aryl (C_1-C_8) alkyl, cycloalkyl (C_1-C_8) alkyl, heterocyclo (C_1-C_8) alkyl, arylhetero (C_1-C_8) alkyl and heteroaryl; and

R^6 is selected from the group consisting of halogen, (C_1-C_4) alkyl, perfluoro (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl (C_1-C_4) alkyl, CN, CO_2R' , $CONR'R''$, $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$, $S(O)_mNR'R''$, $S(O)_mR'$, or $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1 to 2, or R^6 may be combined with R^5 to form an additional 5-, 6-, 7- or 8-membered ring.

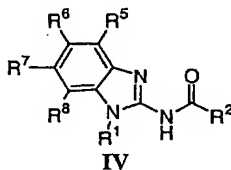
39. The compound of Claim 1, having the formula (III):



wherein

J, K, L and M are independently selected from the group consisting of CR^aR^b , NR^a and O, wherein R^a and R^b are independently selected from the group consisting of H, halogen, CN, CO_2R' , $CONR'R''$, (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl, heteroaryl, $NR'R''$ and OR' , or, J, K, L or M may be combined with an adjacent R group selected from the group consisting of R^1 , R^a and R^b to form an additional 5-, 6-, 7- or 8-membered ring.

40. The compound of Claim 39, having the formula (IV):



wherein

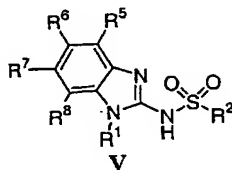
R^5 , R^6 , R^7 and R^8 are independently selected from the group consisting of H, halogen, (C_1-C_4) alkyl, perfluoro (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl, aryl (C_1-C_4) alkyl, heteroaryl, CN, CO_2R' , $CONR'R''$, $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$, $S(O)_mNR'R''$, $S(O)_mR'$, and $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1 to 2, or R^5 , R^6 , R^7 or R^8 may be combined with an adjacent R group selected from the group consisting of R^1 , R^5 , R^6 , R^7 and R^8 to form an additional 5-, 6-, 7- or 8-membered ring.

41. The compound of Claim 40, wherein

R^1 is selected from the group consisting of (C_1-C_8) alkyl, hetero (C_1-C_8) alkyl, fluoro (C_1-C_4) alkyl, cycloalkyl (C_1-C_8) alkyl, heterocyclo (C_1-C_8) alkyl, aryl, aryl (C_1-C_8) alkyl, arylhetero (C_1-C_8) alkyl and heteroaryl; and

R^6 is selected from the group consisting of halogen, (C_1-C_4) alkyl, perfluoro (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl (C_1-C_4) alkyl, CN, CO_2R' , $CONR'R''$, $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$, $S(O)_mNR'R''$, $S(O)_mR'$ and $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1 to 2, or R^6 may be combined with R^5 or R^7 to form an additional 5-, 6-, 7- or 8-membered ring.

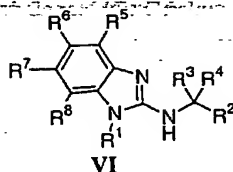
42. The compound of Claim 39, having the formula (V):



wherein

R^5 , R^6 , R^7 and R^8 are independently selected from the group consisting of H, halogen, (C_1-C_4) alkyl, perfluoro (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl, aryl (C_1-C_4) alkyl, heteroaryl, CN, CO_2R' , $CONR'R''$, $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$, $S(O)_mNR'R''$, $S(O)_mR'$ and $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1 to 2, or R^5 , R^6 , R^7 or R^8 may be combined with an adjacent R group selected from the group consisting of R^1 , R^5 , R^6 , R^7 and R^8 to form an additional 5-, 6-, 7- or 8-membered ring.

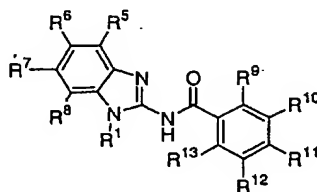
43. The compound of Claim 39, having the formula (VI):



wherein

R^5 , R^6 , R^7 and R^8 are independently selected from the group consisting of H, halogen, (C_1-C_4) alkyl, perfluoro (C_1-C_4) alkyl, (C_1-C_4) heteroalkyl, aryl, aryl (C_1-C_4) alkyl, heteroaryl, CN, CO_2R' , $CONR'R''$, $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$, $S(O)_mNR'R''$, $S(O)_mR'$ and $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1 to 2, or R^5 , R^6 , R^7 or R^8 may be combined with an adjacent R group selected from the group consisting of R^1 , R^5 , R^6 , R^7 and R^8 to form an additional 5-, 6-, 7- or 8-membered ring.

44. The compound of Claim 39, having the formula (VII):



VII

wherein

R^9 , R^{10} , R^{11} , R^{12} and R^{13} are independently selected from the group consisting of H, halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl, aryl(C₁-C₄)alkyl, heteroaryl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR', and N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R^9 , R^{10} , R^{11} , R^{12} or R^{13} may be combined with an adjacent R group selected from the group consisting of R^9 , R^{10} , R^{11} , R^{12} and R^{13} to form an additional 5-, 6-, 7- or 8-membered ring.

45. The compound of Claim 44, wherein

R^1 is selected from the group consisting of (C₁-C₈)alkyl, hetero(C₁-C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl, aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl and heteroaryl; and

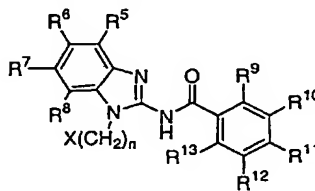
R^6 is selected from the group consisting of halogen, (C₁-C₄)alkyl, perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'', NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'', S(O)_mNR'R'', S(O)_mR', or N(R'')S(O)_mR', wherein the subscript m is an integer from 1 to 2, or R^6 may be combined with R^5 or R^7 to form an additional 5-, 6-, 7- or 8-membered ring.

46. The compound of Claim 44, wherein R^1 is (C₁-C₈)alkyl or (C₁-C₈)heteroalkyl.

47. The compound of Claim 44, wherein R^1 is substituted (C₁-C₈)alkyl or substituted hetero(C₁-C₈)alkyl.

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- 1 48. The compound of Claim 44, wherein, R^1 is (C_1-C_8) alkyl substituted
2 with OR' , $NR'R''$, $OC(O)R'$, CO_2R' , $CONR'R''$, $OC(O)NR'R''$, $NR''C(O)R'$ or
3 $NR''CO_2R'$.
- 1 49. The compound of Claim 44, wherein, R^1 is (C_1-C_8) alkyl substituted
2 with OH.
- 1 50. The compound of Claim 44, wherein R^1 is cycloalkyl or
2 heterocycloalkyl.
- 1 51. The compound of Claim 44, wherein R^1 is substituted cycloalkyl or
2 substituted heterocycloalkyl.
- 1 52. The compound of Claim 44, wherein R^1 is cycloalkyl substituted
2 with OR' , $NR'R''$, $OC(O)R'$, CO_2R' , $CONR'R''$, $OC(O)NR'R''$, $NR''C(O)R'$ or
3 $NR''CO_2R'$.
- 1 53. The compound of Claim 44, wherein R^1 is cycloalkyl substituted
2 with OH.
- 1 54. The compound of Claim 44, wherein R^1 is cyclohexyl.
- 1 55. The compound of Claim 44, wherein R^1 is tetrahydropyranyl.
- 1 56. The compound of Claim 44, wherein at least one of R^9 , R^{10} , R^{11} ,
2 R^{12} and R^{13} is NO_2 .
- 1 57. The compound of Claim 44, having the formula (VIIa):



VIIa

2 wherein

3 the subscript n is an integer from 1 to 5; and

5 X is selected from the group consisting of OR', NR'R'', OC(O)R', CO₂R',
6 CONR'R'', OC(O)NR'R'', NR''C(O)R' and NR''CO₂.

1 58. The compound of Claim 57, wherein X is OH.

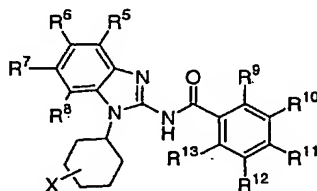
1 59. The compound of Claim 57, wherein at least one of R⁹, R¹⁰, R¹¹,
2 R¹² and R¹³ is NO₂.

1 60. The compound of Claim 57, wherein

2 R¹ is selected from the group consisting of (C₁-C₈)alkyl, hetero(C₁-
3 C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl,
4 aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl and heteroaryl; and

5 R⁶ is selected from the group consisting of halogen, (C₁-C₄)alkyl,
6 perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'',
7 NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'',
8 S(O)_mNR'R'', S(O)_mR' and N(R'')S(O)_mR', wherein the subscript m is an integer from 1
9 to 2, or R⁶ may be combined with R⁵ or R⁷ to form an additional 5-, 6-, 7- or 8-membered
10 ring.

1 61. The compound of Claim 44, having the formula (VIIb):



VIIb

2 wherein X is selected from the group consisting of OR', NR'R'', OC(O)R', CO₂R',
3 CONR'R'', OC(O)NR'R'', NR''C(O)R' and NR''CO₂.

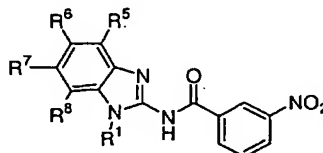
1 62. The compound of Claim 61, wherein X is OH.

1 63. The compound of Claim 61, wherein at least one of R⁹, R¹⁰, R¹¹,
2 R¹² and R¹³ is NO₂.

1 64. The compound of Claim 61, wherein

- 2 R^1 is selected from the group consisting of (C_1-C_8) alkyl, hetero(C_1-
3 C_8)alkyl, fluoro(C_1-C_4)alkyl, cycloalkyl(C_1-C_8)alkyl, heterocyclo(C_1-C_8)alkyl, aryl,
4 aryl(C_1-C_8)alkyl, arylhetero(C_1-C_8)alkyl and heteroaryl; and
5 R^6 is selected from the group consisting of halogen, (C_1-C_4) alkyl,
6 perfluoro(C_1-C_4)alkyl, (C_1-C_4) heteroalkyl, aryl(C_1-C_4)alkyl, CN, CO_2R' , $CONR'R''$,
7 $NR'R''$, NO_2 , OR' , SR' , $C(O)R'$, $N(R'')C(O)R'$, $N(R'')CO_2R'$, $N(R'')C(O)NR'R''$,
8 $S(O)_mNR'R''$, $S(O)_mR'$ and $N(R'')S(O)_mR'$, wherein the subscript m is an integer from 1
9 to 2, or R^6 may be combined with R^5 or R^7 to form an additional 5-, 6-, 7- or 8-membered
10 ring.

1 65. The compound of Claim 44, having the formula (VIIc):



VIIc

- 2
1 66. The compound of Claim 65, wherein R^1 is (C_1-C_8) alkyl or $(C_1-$
2 $C_8)$ heteroalkyl.
1 67. The compound of Claim 65, wherein R^1 is substituted (C_1-C_8) alkyl
2 or substituted (C_1-C_8) heteroalkyl.
1 68. The compound of Claim 65, wherein R^1 is (C_1-C_8) alkyl substituted
2 with OR' , $NR'R''$, $OC(O)R'$, CO_2R' , $CONR'R''$, $OC(O)NR'R''$, $NR''C(O)R'$ or
3 $NR''CO_2R'$.
1 69. The compound of Claim 65, wherein R^1 is (C_1-C_8) alkyl substituted
2 with OH.
1 70. The compound of Claim 65, wherein R^1 is cycloalkyl or
2 heterocycloalkyl.
1 71. The compound of Claim 65, wherein R^1 is substituted cycloalkyl or
2 substituted heterocycloalkyl.

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- 1 72. The compound of Claim 65, wherein R¹ is cycloalkyl substituted
2 with OR', NR'R'', OC(O)R', CO₂R', CONR'R'', OC(O)NR'R'', NR''C(O)R' or
3 NR''CO₂R'.
- 1 73. The compound of Claim 65, wherein R¹ is cycloalkyl substituted
2 with OH.
- 1 74. The compound of Claim 65, wherein R¹ is cyclohexyl.
- 1 75. The compound of Claim 65, wherein R¹ is tetrahydropyranyl.
- 1 76. The compound of Claim 65, wherein
2 R¹ is selected from the group consisting of (C₁-C₈)alkyl, hetero(C₁-
3 C₈)alkyl, fluoro(C₁-C₄)alkyl, cycloalkyl(C₁-C₈)alkyl, heterocyclo(C₁-C₈)alkyl, aryl,
4 aryl(C₁-C₈)alkyl, arylhetero(C₁-C₈)alkyl and heteroaryl; and
5 R⁶ is selected from the group consisting of halogen, (C₁-C₄)alkyl,
6 perfluoro(C₁-C₄)alkyl, (C₁-C₄)heteroalkyl, aryl(C₁-C₄)alkyl, CN, CO₂R', CONR'R'',
7 NR'R'', NO₂, OR', SR', C(O)R', N(R'')C(O)R', N(R'')CO₂R', N(R'')C(O)NR'R'',
8 S(O)_mNR'R'', S(O)_mR' and N(R'')S(O)_mR', wherein the subscript m is an integer from 1
9 to 2, or R⁶ may be combined with R⁵ or R⁷ to form an additional 5-, 6-, 7- or 8-membered
10 ring.
- 1 77. A pharmaceutical composition comprising a pharmaceutically
2 acceptable carrier or excipient and a compound of Claim 1.
- 1 78. The composition of Claim 77, comprising a pharmaceutically
2 acceptable carrier or excipient and a compound of any one of Claims 2-76.
- 1 79. A method of treating a condition or disorder mediated by IRAK,
2 comprising
3 administering to a subject in need of such treatment a therapeutically
4 effective amount of the compound of Claim 1.
- 1 80. The method of Claim 79, wherein said condition or disorder is
2 selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease,
3 allergic disease, psoriasis, asthma, multiple sclerosis, graft rejection and sepsis.

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1 81. The method of Claim 79, wherein said condition or disorder is
2 rheumatoid arthritis.

3 82. The method of Claim 79, wherein said condition or disorder is
4 inflammatory bowel disease.

5 83. The method of Claim 79, wherein said condition or disorder is
6 multiple sclerosis.

1 84. The method of Claim 79, wherein said compound is administered
2 orally, parenterally or topically.

1 85. The method of Claim 79, wherein said compound is administered
2 in combination with a therapeutic agent selected from the group consisting of
3 methotrexate, sulfasalazine, a COX-2 inhibitor, hydroxychloroquine, cyclosporine A, D-
4 penicillamine, infliximab, etanercept, auranofin and aurothioglucose.

1 86. The method of Claim 79, wherein said compound is administered
2 in combination with a therapeutic agent selected from the group consisting of
3 sulfasalazine, sulfasalazine analogs, mesalamine, corticosteroids, corticosteroid analogs,
4 azathioprine, 6-mercaptopurine, cyclosporine A, methotrexate and infliximab.

1 87. The method of Claim 79, wherein said compound is administered
2 in combination with a therapeutic agent selected from the group consisting of interferon
3 β -1 β , interferon β -1 α , azathioprine, glatiramer acetate, a glucocorticoid and
4 cyclophosphamide.

1 88. The method of Claim 79, wherein said subject is a human.

1 89. The method of Claim 79, wherein said compound modulates
2 IRAK.

1 90. A method for treating a condition or disorder mediated by IRAK,
2 comprising
3 administering to a subject in need thereof a therapeutically effective
4 amount of a compound of Claim 1.

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1 **91.** A method for treating a condition or disorder mediated by NF- κ B,
2 comprising
3 administering to a subject in need of such treatment a therapeutically
4 effective amount of the compound of Claim 1.

1 **92.** The method of Claim 90 or 91, wherein said condition or disorder
2 is selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease,
3 allergic disease, psoriasis, asthma, multiple sclerosis, graft rejection and sepsis.

1 **93.** A method for modulating IRAK, comprising
2 contacting a cell with a compound of Claim 1.

1 **94.** A method for decreasing NF- κ B activation, comprising
2 contacting a cell with a compound of Claim 1.

1 **95.** A method for modulating IRAK, comprising
2 contacting an IRAK protein with a compound of Claim 1.

1 **96.** The method of Claim 95, wherein said compound inhibits IRAK.

1 **97.** The method of Claim 95, wherein said compound activates IRAK.

BENZIMIDAZOLE DERIVATIVES

ABSTRACT OF THE DISCLOSURE

Compounds, compositions and methods are provided that are useful in the treatment of inflammatory and immune-related conditions or disorders. In particular, the invention provides compounds which modulate the expression and/or function of proteins involved in inflammation and immune response regulation. The subject compounds are 2-aminoimidazole derivatives.

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Ser Gly Ala Ala Pro Trp Gln Pro Leu Ala Ala Pro Ser Gly Ala Ser	
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gcc cag gca gca gag cag ctg cag aga ggc ccc aac cag ccc gtg gag	1840
Ala Gln Ala Ala Glu Gln Leu Gln Arg Gly Pro Asn Gln Pro Val Glu	
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Ser Asp Glu Ser Leu Gly Gly Leu Ser Ala Ala Leu Arg Ser Trp His	
590 595 600	
ttg act cca agc tgc cct ctg gac cca gca ccc ctc agg gag gcc ggc	1936
Leu Thr Pro Ser Cys Pro Leu Asp Pro Ala Pro Leu Arg Glu Ala Gly	
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tgt cct cag ggg gac acg gca gga gaa tcg agc tgg ggg agt ggc cca	1984
Cys Pro Gln Gly Asp Thr Ala Gly Glu Ser Ser Trp Gly Ser Gly Pro	
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gga tcc cgg ccc aca gcc gtg gaa gga ctg gcc ctt ggc agc tct gca	2032
Gly Ser Arg Pro Thr Ala Val Glu Gly Leu Ala Leu Gly Ser Ser Ala	
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Ser Ser Ser Ser Glu Pro Pro Gln Ile Ile Ile Asn Pro Ala Arg Gln	
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Lys Met Val Gln Lys Leu Ala Leu Tyr Glu Asp Gly Ala Leu Asp Ser	
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Leu Gln Leu Leu Ser Ser Ser Ser Leu Pro Gly Leu Gly Leu Glu Gln	
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Asp Arg Gln Gly Pro Glu Glu Ser Asp Glu Phe Gln Ser	
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Val Met Asp Ala Leu Glu Pro Ala Asp Trp Cys Gln Phe Ala Ala Leu
35 40 45

Ile Val Arg Asp Gln Thr Glu Leu Arg Leu Cys Glu Arg Ser Gly Gln
50 55 60

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Arg Thr Ala Ser Val Leu Trp Pro Trp Ile Asn Arg Asn Ala Arg Val
65 70 75 80

Ala Asp Leu Val His Ile Leu Thr His Leu Gln Leu Leu Arg Ala Arg
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Asp Ile Ile Thr Ala Trp His Pro Pro Ala Pro Leu Pro Ser Pro Gly
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Thr Thr Ala Pro Arg Pro Ser Ser Ile Pro Ala Pro Ala Glu Ala Glu
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Ala Trp Ser Pro Arg Lys Leu Pro Ser Ser Ala Ser Thr Phe Leu Ser
130 135 140

Pro Ala Phe Pro Gly Ser Gln Thr His Ser Gly Pro Glu Leu Gly Leu
145 150 155 160

Val Pro Ser Pro Ala Ser Leu Trp Pro Pro Pro Pro Ser Pro Ala Pro
165 170 175

Ser Ser Thr Lys Pro Gly Pro Glu Ser Ser Val Ser Leu Leu Gln Gly
180 185 190

Ala Arg Pro Ser Pro Phe Cys Trp Pro Leu Cys Glu Ile Ser Arg Gly
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Thr His Asn Phe Ser Glu Glu Leu Lys Ile Gly Glu Gly Gly Phe Gly
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Cys Val Tyr Arg Ala Val Met Arg Asn Thr Val Tyr Ala Val Lys Arg
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Leu Lys Glu Asn Ala Asp Leu Glu Trp Thr Ala Val Lys Gln Ser Phe
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Leu Thr Glu Val Glu Gln Leu Ser Arg Phe Arg His Pro Asn Ile Val
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Asp Phe Ala Gly Tyr Cys Ala Gln Asn Gly Phe Tyr Cys Leu Val Tyr
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Gly Phe Leu Pro Asn Gly Ser Leu Glu Asp Arg Leu His Cys Gln Thr
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Gln Ala Cys Pro Pro Leu Ser Trp Pro Gln Arg Leu Asp Ile Leu Leu
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Gly Thr Ala Arg Ala Ile Gln Phe Leu His Gln Asp Ser Pro Ser Leu
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Ile His Gly Asp Ile Lys Ser Ser Asn Val Leu Leu Asp Glu Arg Leu
340 345 350

Thr Pro Lys Leu Gly Asp Phe Gly Leu Ala Arg Phe Ser Arg Phe Ala
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Gly Ser Ser Pro Ser Gln Ser Ser Met Val Ala Arg Thr Gln Thr Val
370 375 380

Arg Gly Thr Leu Ala Tyr Leu Pro Glu Glu Tyr Ile Lys Thr Gly Arg
385 390 395 400

Leu Ala Val Asp Thr Asp Thr Phe Ser Phe Gly Val Val Val Leu Glu
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Thr Leu Ala Gly Gln Arg Ala Val Lys Thr His Gly Ala Arg Thr Lys
420 425 430

Tyr Leu Lys Asp Leu Val Glu Glu Glu Ala Glu Glu Ala Gly Val Ala
435 440 445

Leu Arg Ser Thr Gln Ser Thr Leu Gln Ala Gly Leu Ala Ala Asp Ala
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Trp Ala Ala Pro Ile Ala Met Gln Ile Tyr Lys Lys His Leu Asp Pro
465 470 475 480

Arg Pro Gly Pro Cys Pro Pro Glu Leu Gly Leu Gly Leu Gly Gln Leu
485 490 495

Ala Cys Cys Cys Leu His Arg Arg Ala Lys Arg Arg Pro Pro Met Thr
500 505 510

Gln Val Tyr Glu Arg Leu Glu Lys Leu Gln Ala Val Val Ala Gly Val
515 520 525

Pro Gly His Leu Glu Ala Ala Ser Cys Ile Pro Pro Ser Pro Gln Glu
530 535 540

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Asn Ser Tyr Val Ser Ser Thr Gly Arg Ala His Ser Gly Ala Ala Pro
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Trp Gln Pro Leu Ala Ala Pro Ser Gly Ala Ser Ala Gln Ala Ala Glu
565 570 575

Gln Leu Gln Arg Gly Pro Asn Gln Pro Val Glu Ser Asp Glu Ser Leu
580 585 590

Gly Gly Leu Ser Ala Ala Leu Arg Ser Trp His Leu Thr Pro Ser Cys
595 600 605

Pro Leu Asp Pro Ala Pro Leu Arg Glu Ala Gly Cys Pro Gln Gly Asp
610 615 620

Thr Ala Gly Glu Ser Ser Trp Gly Ser Gly Pro Gly Ser Arg Pro Thr
625 630 635 640

Ala Val Glu Gly Leu Ala Leu Gly Ser Ser Ala Ser Ser Ser Ser Glu
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Pro Pro Gln Ile Ile Ile Asn Pro Ala Arg Gln Lys Met Val Gln Lys
660 665 670

Leu Ala Leu Tyr Glu Asp Gly Ala Leu Asp Ser Leu Gln Leu Leu Ser
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Gly Leu Ile Arg Lys Leu Ser Asp Phe Ile Asp Pro Gln Glu Gly Trp
20 25 30

aag aag tta gct gta gct att aaa aaa cca tct ggt gat gat aga tac 144
Lys Lys Leu Ala Val Ala Ile Lys Lys Pro Ser Gly Asp Asp Arg Tyr
35 40 45

aat cag ttt cac ata agg aga ttt gaa gca tta ctt caa act gga aaa 192
Asn Gln Phe His Ile Arg Arg Phe Glu Ala Leu Leu Gln Thr Gly Lys
50 55 60

agt ccc act tct gaa tta ctg ttt gac tgg ggc acc aca aat tgc aca 240
Ser Pro Thr Ser Glu Leu Leu Phe Asp Trp Gly Thr Thr Asn Cys Thr
65 70 75 80

gct ggt gat ctt gtg gat ctt ttg atc caa aat gaa ttt ttt gct cct 288
Ala Gly Asp Leu Val Asp Leu Leu Ile Gln Asn Glu Phe Phe Ala Pro
85 90 95

gcg agt ctt ttg ctc cca gat gct gtt ccc aaa act gct aat aca cta 336
Ala Ser Leu Leu Leu Pro Asp Ala Val Pro Lys Thr Ala Asn Thr Leu
100 105 110

cct tct aaa gaa gct ata aca gtt cag caa aaa cag atg cct ttc tgt 384
Pro Ser Lys Glu Ala Ile Thr Val Gln Gln Lys Gln Met Pro Phe Cys
115 120 125

gac aaa gac agg aca ttg atg aca cct gtg cag aat ctt gaa caa agc 432
Asp Lys Asp Arg Thr Leu Met Thr Pro Val Gln Asn Leu Glu Gln Ser
130 135 140

tat atg cca cct gac tcc tca agt cca gaa aat aaa agt tta gaa gtt 480
Tyr Met Pro Pro Asp Ser Ser Ser Pro Glu Asn Lys Ser Leu Glu Val
145 150 155 160

agt gat aca cgt ttt cac agt ttt tca ttt tat gaa ttg aag aat gtc 528
Ser Asp Thr Arg Phe His Ser Phe Ser Phe Tyr Glu Leu Lys Asn Val
165 170 175

aca aat aac ttt gat gaa cga ccc att tct gtt ggt ggt aat aaa atg 576
Thr Asn Asn Phe Asp Glu Arg Pro Ile Ser Val Gly Gly Asn Lys Met
180 185 190

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Gly Glu Gly Gly Phe Gly Val Val Tyr Lys Gly Tyr Val Asn Asn Thr
195 200 205

act gtg gca gtg aag aag ctt gca gca atg gtt gac att act act gaa 672
Thr Val Ala Val Lys Lys Leu Ala Ala Met Val Asp Ile Thr Thr Glu
210 215 220

gaa ctg aaa cag cag ttt gat caa gaa ata aaa gta atg gca aag tgt 720
9

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Gln	His	Glu	Asn	Leu	Val	Glu	Leu	Leu	Met	Gly	Phe	Ser	Ser	Asp	Gly	Asp	
				245					250					255			
gac	ctc	tgc	tta	gta	tat	gtt	tac	atg	cct	aat	ggt	tca	ttg	cta	gac		816
Asp	Leu	Cys	Leu	Val	Tyr	Val	Tyr	Met	Pro	Asn	Gly	Ser	Leu	Leu	Asp		
			260					265					270				
aga	ctc	tct	tgc	ttg	gat	ggt	act	cca	cca	ctt	tct	tggt	cac	atg	aga		864
Arg	Leu	Ser	Cys	Leu	Asp	Gly	Thr	Pro	Pro	Leu	Ser	Trp	His	Met	Arg		
			275				280					285					
tgc	aag	att	gct	cag	ggt	gca	gct	aat	ggc	atc	aat	ttt	cta	cat	gaa		912
Cys	Lys	Ile	Ala	Gln	Gly	Ala	Ala	Asn	Gly	Ile	Asn	Phe	Leu	His	Glu		
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aat	cat	cat	att	cat	aga	gat	att	aaa	agt	gca	aat	atc	tta	ctg	gat		960
Asn	His	His	Ile	His	Arg	Asp	Ile	Lys	Ser	Ala	Asn	Ile	Leu	Leu	Asp		
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gaa	gct	ttt	act	gct	aaa	ata	tct	gac	ttt	ggc	ctt	gca	cgg	gct	tct		1008
Glu	Ala	Phe	Thr	Ala	Lys	Ile	Ser	Asp	Phe	Gly	Leu	Ala	Arg	Ala	Ser		
				325					330					335			
gag	aag	ttt	gcc	cag	aca	gtc	atg	act	agc	aga	att	gtg	gga	aca	aca		1056
Glu	Lys	Phe	Ala	Gln	Thr	Val	Met	Thr	Ser	Arg	Ile	Val	Gly	Thr	Thr		
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Ala	Tyr	Met	Ala	Pro	Glu	Ala	Leu	Arg	Gly	Glu	Ile	Thr	Pro	Lys	Ser		
		355				360						365					
gat	att	tac	agc	ttt	ggt	gtg	gtt	tta	cta	gaa	ata	ata	act	gga	ctt		1152
Asp	Ile	Tyr	Ser	Phe	Gly	Val	Val	Leu	Leu	Glu	Ile	Ile	Thr	Gly	Leu		
					375						380						
cca	gct	gtg	gat	gaa	cac	cgt	gaa	cct	cag	tta	ttg	cta	gat	att	aaa		1200
Pro	Ala	Val	Asp	Glu	His	Arg	Glu	Pro	Gln	Leu	Leu	Leu	Asp	Ile	Lys		
					390					395					400		
gaa	gaa	att	gaa	gat	gaa	gaa	aag	aca	att	gaa	gat	tat	att	gat	aaa		1248
Glu	Glu	Ile	Glu	Asp	Glu	Glu	Lys	Thr	Ile	Glu	Asp	Tyr	Ile	Asp	Lys		
				405					410					415			
aag	atg	aat	gat	gct	gat	tcc	act	tca	gtt	gaa	gct	atg	tac	tct	gtt		1296
Lys	Met	Asn	Asp	Ala	Asp	Ser	Thr	Ser	Val	Glu	Ala	Met	Tyr	Ser	Val		
			420				425						430				
gct	agt	caa	tgt	ctg	cat	gaa	aag	aaa	aat	aag	aga	cca	gac	att	aag		1344
Ala	Ser	Gln	Cys	Leu	His	Glu	Lys	Lys	Asn	Lys	Arg	Pro	Asp	Ile	Lys		
			435				440					445					
aag	gtt	caa	cag	ctg	ctg	caa	gag	atg	aca	gct	tct	taa					1383
Lys	Val	Gln	Gln	Leu	Leu	Gln	Glu	Met	Thr	Ala	Ser						
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<213> Homo sapiens

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20 25 30

Lys Lys Leu Ala Val Ala Ile Lys Lys Pro Ser Gly Asp Asp Arg Tyr
35 40 45

Asn Gln Phe His Ile Arg Arg Phe Glu Ala Leu Leu Gln Thr Gly Lys
50 55 60

Ser Pro Thr Ser Glu Leu Leu Phe Asp Trp Gly Thr Thr Asn Cys Thr
65 70 75 80

Ala Gly Asp Leu Val Asp Leu Leu Ile Gln Asn Glu Phe Phe Ala Pro
85 90 95

Ala Ser Leu Leu Leu Pro Asp Ala Val Pro Lys Thr Ala Asn Thr Leu
100 105 110

Pro Ser Lys Glu Ala Ile Thr Val Gln Gln Lys Gln Met Pro Phe Cys
115 120 125

Asp Lys Asp Arg Thr Leu Met Thr Pro Val Gln Asn Leu Glu Gln Ser
130 135 140

Tyr Met Pro Pro Asp Ser Ser Ser Pro Glu Asn Lys Ser Leu Glu Val
145 150 155 160

Ser Asp Thr Arg Phe His Ser Phe Ser Phe Tyr Glu Leu Lys Asn Val
165 170 175

Thr Asn Asn Phe Asp Glu Arg Pro Ile Ser Val Gly Gly Asn Lys Met
180 185 190

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Gly Glu Gly Gly Phe Gly Val Val Tyr Lys Gly Tyr Val Asn Asn Thr
195 200 205

Thr Val Ala Val Lys Lys Leu Ala Ala Met Val Asp Ile Thr Thr Glu
210 215 220

Glu Leu Lys Gln Gln Phe Asp Gln Glu Ile Lys Val Met Ala Lys Cys
225 230 235 240

Gln His Glu Asn Leu Val Glu Leu Leu Gly Phe Ser Ser Asp Gly Asp
245 250 255

Asp Leu Cys Leu Val Tyr Val Tyr Met Pro Asn Gly Ser Leu Leu Asp
260 265 270

Arg Leu Ser Cys Leu Asp Gly Thr Pro Pro Leu Ser Trp His Met Arg
275 280 285

Cys Lys Ile Ala Gln Gly Ala Ala Asn Gly Ile Asn Phe Leu His Glu
290 295 300

Asn His His Ile His Arg Asp Ile Lys Ser Ala Asn Ile Leu Leu Asp
305 310 315 320

Glu Ala Phe Thr Ala Lys Ile Ser Asp Phe Gly Leu Ala Arg Ala Ser
325 330 335

Glu Lys Phe Ala Gln Thr Val Met Thr Ser Arg Ile Val Gly Thr Thr
340 345 350

Ala Tyr Met Ala Pro Glu Ala Leu Arg Gly Glu Ile Thr Pro Lys Ser
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Asp Ile Tyr Ser Phe Gly Val Val Leu Leu Glu Ile Ile Thr Gly Leu
370 375 380

Pro Ala Val Asp Glu His Arg Glu Pro Gln Leu Leu Leu Asp Ile Lys
385 390 395 400

Glu Glu Ile Glu Asp Glu Glu Lys Thr Ile Glu Asp Tyr Ile Asp Lys
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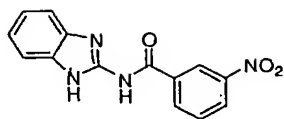
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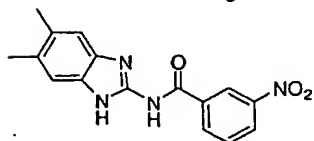
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FIG. 1a

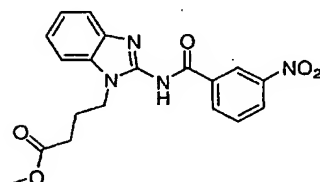
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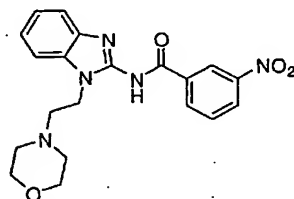
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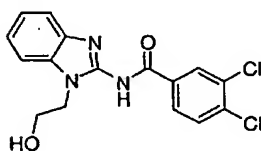
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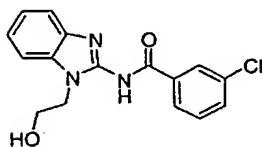
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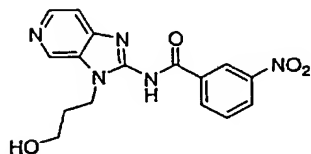
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19



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FIG. 1b

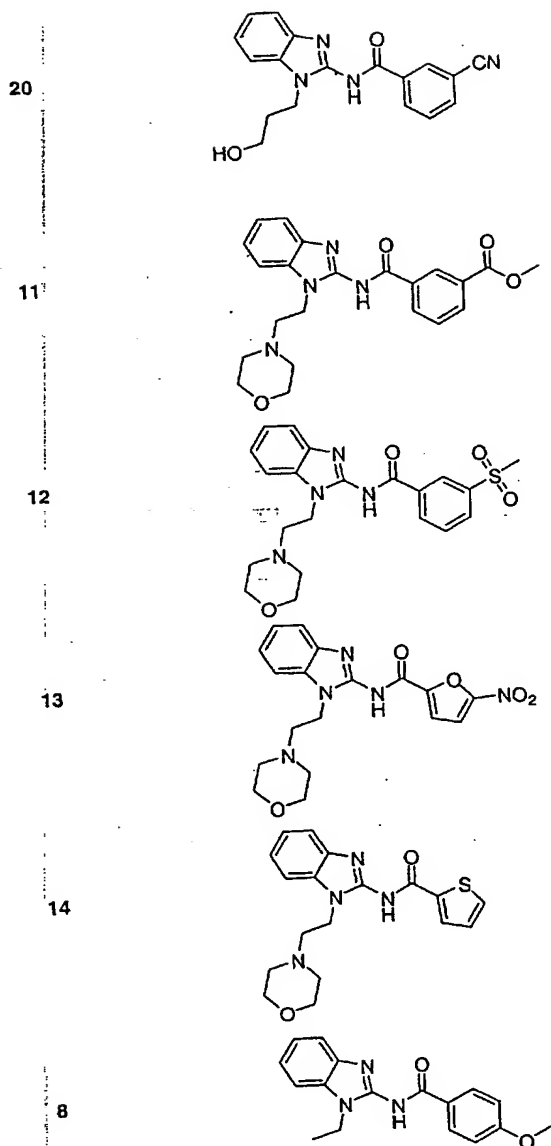
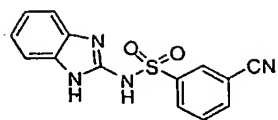
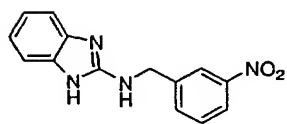


FIG. 1c

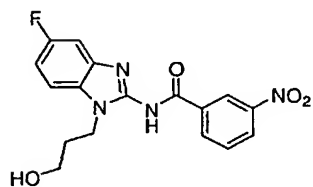
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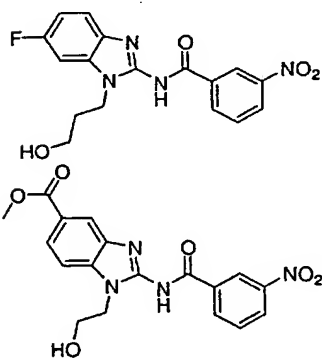
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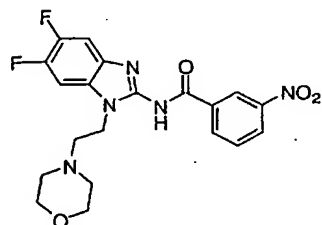


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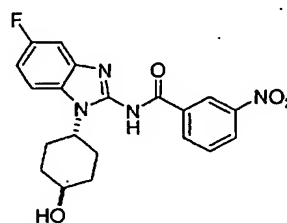
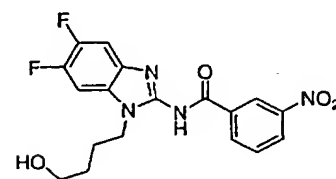
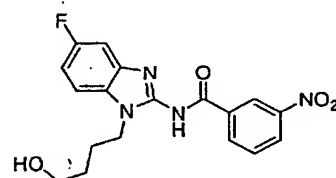
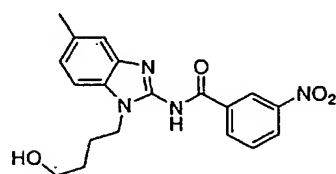
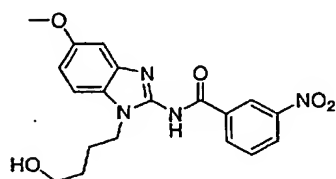
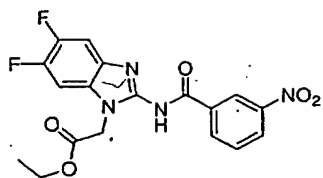
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FIG. 1d

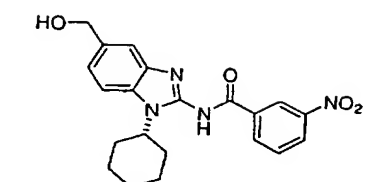


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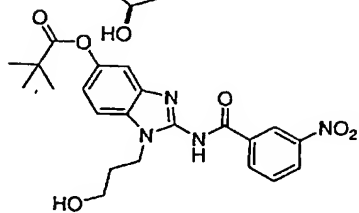
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FIG. 1e

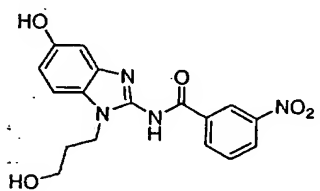
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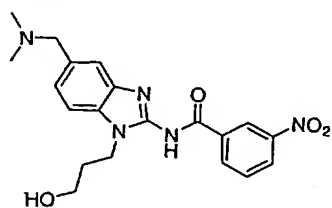
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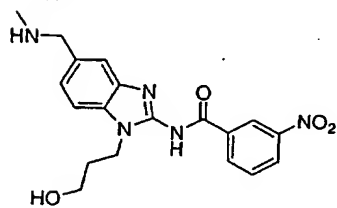
29



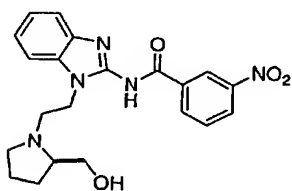
30



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